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SULFUROS CLÚSTER DE MOLIBDENO COMO CATALIZADORES SELECTIVOS EN PROCESOS DE REDUCCIÓN PARA LA SÍNTESIS DE AMINAS

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TESIS DOCTORAL

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ROSA Mª LLUSAR BARELLES, CATEDRÁTICA DEL ÁREA DE QUÍMICA FÍSICA DE LA UNIVERSITAT JAUME I, E IVÁN SORRIBES TERRÉS, INVESTIGADOR POSTDOCTORAL EN EL INSTITUTO DE TECNOLOGÍA QUÍMICA DE LA UNIVERSITAT POLITÈCNICA DE VALÈNCIA

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Y para que conste a los efectos oportunos, firmamos el presente certificado en Castellón a 22 de Junio de 2017.

Prof. Rosa Mª Llusar Barelles

Dr. Iván Sorribes Terrés

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Hace 10 años decidí estudiar Licenciatura Química en la UJI, y esa decisión no solamente me ha hecho llegar hasta aquí, sino que me permitió conocer a mis químic@s favorit@s Olga, Emma, Lidón, Miguel Ángel y Sara. La amistad que forjamos durante los años de carrera es sincera y para siempre y, en esta etapa de tesis, he sentido todo vuestro apoyo y confianza en mí ¡Gracias!

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RESUMEN

En esta tesis doctoral se describe la síntesis, caracterización estructural y aplicaciones catalíticas de nuevos sulfuros clúster de molibdeno funcionalizados con ligandos dadores de nitrógeno. En el Capítulo 1 se introduce una visión histórica de los procesos catalíticos, enfatizando aquellos hechos que consideramos relevantes en el contexto de la catálisis basada en clústeres. En este capítulo, se incluye también una introducción general a la química de clústeres centrada en los sulfuros metálicos. A continuación, en el Capítulo 2 se enumeran los objetivos de este trabajo.

La síntesis y caracterización del primer clúster diamino Mo_3S_4 de fórmula $[Mo_3S_4Cl_3(dmen)_3]^+$ (dmen = *N,N'*-dimetiletilendiamina) se describe en el Capítulo 3, y se demuestra la actividad de este nuevo complejo en la reducción de nitro- y azoarenos para producir anilinas utilizando silanos como agentes reductores. También se evalúa la selectividad del catalizador y, a través de la monitorización de la reacción mediante la técnica de infusión de muestra presurizada en combinación con espectrometría de masas, se confirma que se trata de catálisis mediada por clústeres.

La utilización del complejo de tiourea $[Mo_3S_4(tu)_8(H_2O)]^{4+}$ como precursor para la funcionalización de la unidad Mo_3S_4 con ligandos dadores de nitrógeno se describe en el Capítulo 4. Los complejos diamino $[Mo_3S_4Cl_3(dmen)_3]^+$ y diimino $[Mo_3S_4Cl_3(dnbpy)_3]^+$ (dnbpy = 4,4'-dinonil-2,2'-bipiridil) que se obtienen a partir del derivado de tiourea anteriormente nombrado, se prueban en la reducción de nitroarenos con hidrógeno molecular, considerado el agente reductor más respetuoso con el medioambiente. A continuación, se estudia la selectividad del nuevo catalizador diimino, que permite la obtención de una gran variedad de aminas primarias y, mediante técnicas espectrométricas, se demuestra que la integridad del clúster se mantiene durante el proceso catalítico.

La catálisis tándem es una alternativa excelente para el diseño de procesos económicos y sostenibles. En el Capítulo 5, el clúster diamino $[Mo_3S_4Cl_3(dmen)_3]^+$ se utiliza en la aminación reductiva en cascada de aldehídos a partir de nitroarenos con hidrógeno como agente reductor. Así, utilizando materiales de partida baratos y abundantes, se producen de manera selectiva aminas secundarias de gran valor.

El Capítulo 6 se centra en la aplicación del clúster diamino en la síntesis de aminas terciarias. Para dicho objetivo, se sintetiza un clúster heterobimetálico Mo_3PtS_4 a partir del precursor trinuclear. La actividad catalítica del nuevo complejo heterobimetálico $[Mo_3(Pt(PPh_3))S_4Cl_3(dmen)_3]^+$ se evalúa en la metilación de nitroarenos para dar lugar a aminas terciarias utilizando ácido fórmico como fuente renovable de C_1 y silanos como agentes reductores.

El Capítulo 7 contiene una discusión global de todos los resultados descritos en esta tesis. Los procedimientos experimentales utilizados en este trabajo, junto a la caracterización de los compuestos, se incluyen en los capítulos correspondientes. Finalmente, las conclusiones generales de esta tesis doctoral se recogen en el Capítulo 8.

ABSTRACT

This PhD Thesis describes the synthesis, structural characterization and catalytic applications of new molybdenum sulphide clusters bearing nitrogen-donor ligands. Chapter 1 introduces a historical overview of catalysis emphasizing those facts that we consider relevant in the context of cluster catalysis. This chapter also includes a general introduction to cluster chemistry focused on metal sulphide compounds. Then, the main objectives of this work are listed in Chapter 2.

The synthesis and characterization of the first diamino Mo_3S_4 cluster of formula $[Mo_3S_4Cl_3(dmen)_3]^+$ (dmen = *N,N'*-dimethylethylenediamine) is described in Chapter 3, and the activity of this new complex as catalyst for the reduction of nitro and azoarenes to produce anilines using silanes as reducing agents is demonstrated. The selectivity of the catalyst is evaluated and cluster catalysis is proved from reaction monitoring using a pressurized sample infusion (*PSI*) ESI mass spectrometric technique.

The use of the thiourea complex $[Mo_3S_4(tu)_8(H_2O)]^{4+}$ as precursor for the functionalization of the Mo_3S_4 unit with nitrogen-donor ligands is described in Chapter 4. The diamino $[Mo_3S_4Cl_3(dmen)_3]^+$ and diimino $[Mo_3S_4Cl_3(dnbpy)_3]^+$ (dnbpy = 4,4'-dinonyl-2,2'-bipyridyl) complexes obtained from the thiourea precursor are tested in the reduction of nitroarenes with molecular hydrogen, which is known to be the most environmentally benign reducing agent. The chemoselectivity of this new diimino catalyst is evaluated to produce a large variety of primary amines, and mass spectrometry techniques show that the integrity of the cluster is preserved during the catalytic process.

Tandem catalysis is an excellent alternative towards the design of economic and sustainable processes. In chapter 5, the diamino cluster $[Mo_3S_4Cl_3(dmen)_3]^+$ is used for the one-pot reductive amination of aldehydes with nitro compounds using

hydrogen as reductant to selectively produce valuable secondary amines from cheap and abundant starting materials.

Chapter 6 is concerned with the application of the molybdenum sulphide diamino cluster in the synthesis of tertiary amines. For this purpose, an heterobimetallic Mo_3PtS_4 complex is synthesized from the diamino trinuclear precursor. The catalytic activity of the new heterobimetallic $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ cluster is evaluated for the direct methylation of nitroarenes to afford tertiary amines using formic acid as a renewable C_1 source and silanes as reducing agents.

Chapter 7 comprises a global discussion of all the results described in this dissertation. The experimental procedures employed in this work, together with the characterization of the compounds, are included in the corresponding chapters. Finally, the general conclusions of this PhD Thesis are provided in Chapter 8.

ABREVIATURAS

Ar	aromático
aq.	*aqueous*
br	*broad*
ca.	*circa* (aproximadamente)
calcd.	calculado
CCD	*Charge Coupled Device*
CCDC	*Cambridge Christalographic Data Centre*
Conv.	conversión
Cp	ciclopentadienilo
Cp'	metilciclopentadienilo
CSE	*Cluster Skeletal Electrons*
CV	*Cyclic Voltammetry*
d	doblete
dba	1,5-difenil-1,4-pentadien-3-ona *(dibenzylideneacetone)*
dien	dietilentriamina
dmen	*N,N'*-dimetiletilendiamina
dmpe	1,2-bis(dimetilfosfino)etano
dnbpy	4,4'-dinonil-2,2'-bipiridina
DMSO	dimetilsulfóxido
dppe	1,2-bis-(difenilfosfino)etano
dppp	1,3-bis(difenilfosfino)propano
equiv.	equivalentes
ESI	*Electrospray Ionization*
Et	etilo
et. al.	*et alii* (y otros autores)
FA	*Formic Acid*

FID	*Flame Ionization Detector*
GC	*Gas Chromatography*
GC-MS	*Gas Chromatography-Mass Spectrometry*
HSQC	*Heteronuclear Single Quantum Correlation*
i.e.	*id est* (esto es)
^{i}Pr	isopropilo
IR	infrarrojo
L	ligando
m	multiplete
m/z	relación masa/carga
M^+	pico molecular
Me	metilo
min	minutos
MOF	*Metal Organic Frameworks*
MS	*Mass Spectrometry*
$^{n}Bu_4N$	tetrabutilamonio
NHC	carbeno N-heterocíclico
nor	2-norborneno
o-	posición orto
ORTEP	*Oak Ridge Termal-Ellipsoid Plot*
P	presión
p-	posición para
Ph	fenilo
PMHS	polimetilhidrosiloxano
PSI	*Pressurized Sample Infusion*
q	*quadruplet*
RMN	Resonancia Magnética Nuclear
RT	*Room Temperature*

s	singulete
t	triplete
T	temperatura
tacn	triazaciclononano
TBA	tetrabutilamonio
^{t}Bu	t-butilo
THF	tetrahidrofurano
Triphos	1,1,1-tris(difenilfosfinometil)etano
tu	tiourea
u.m.a.	unidad de masa atómica
UV/Vis	ultravioleta/visible
V	volumen

ÍNDICE

1

Introducción

1. Introducción
    1.1 Aspectos generales
    1.2 Bibliografía

"Un científico debe tomarse la libertad de plantear cualquier cuestión, de dudar de cualquier afirmación y de corregir errores."

Robert Oppenheimer

1.1. Aspectos generales

La catálisis emerge como disciplina científica a principios del siglo XX con la concesión del premio Nobel de Química en 1909 a Wilhelm Ostwald, Profesor de Química Física de la Unviversidad de Leipzig en Alemania. El profesor Ostwald fue galardonado por sus investigaciones acerca de los principios fundamentales que gobiernan el equilibrio químico y las velocidades de reacción. En el transcurso de sus estudios cinéticos en disolución acuosa, Ostwald define al catalizador como una sustancia que cambia la velocidad de una reacción sin alterarse durante el proceso. El concepto actual de catalizador restringe esta definición al considerar como tal únicamente aquellas sustancias que aumentan la velocidad descartando la idea de que los inhibidores operen como catalizadores negativos.[1]

En 1913, la Academia Sueca de las Ciencias reconoce las contribuciones de Paul Sabatier, Profesor de Química Orgánica en la Universidad de Toulouse en Francia, otorgándole el premio Nobel por su método para la hidrogenación de compuestos orgánicos en presencia de metales finamente divididos. Este hecho supuso un gran avance en Química Orgánica dada la variedad de procesos que implican la reducción catalítica con hidrógeno. En su discurso de entrega de los premios, Sabatier destaca la hidrogenación del nitrobenceno para la obtención de anilina, un tema clave en el contexto de esta tesis doctoral. Hoy en día, Sabatier es considerado el padre de la Catálisis Moderna por la formulación del denominado "Principio de Sabatier", que sentó las bases para comprender esta disciplina. Dicho principio establece que las mejores propiedades catalíticas se obtienen cuando la fuerza de interacción entre el sustrato y el catalizador alcanza un valor óptimo. Tal como se ilustra en la Figura 1, la velocidad será máxima cuando los enlaces formados entre los reactivos y el catalizador no sean demasiado fuertes como para impedir la posterior liberación del producto ni tan débiles que dificulten la formación del intermedio de reacción.

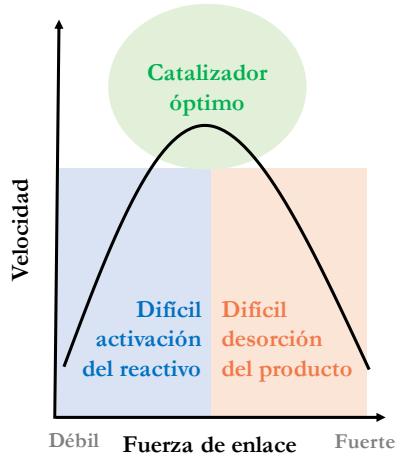


Figura 1. Representación esquemática del Principio de Sabatier.

La catálisis ha aunado diversas disciplinas científicas que a lo largo de la historia se habían desarrollado de manera prácticamente independiente. De hecho, la investigación catalítica se presenta en la actualidad como el área de la ciencia que involucra a más especialidades, algunas de ellas ilustradas en la Figura 2.[2] El trabajo desarrollado en la presente tesis doctoral es un claro ejemplo de esta interdisciplinariedad.

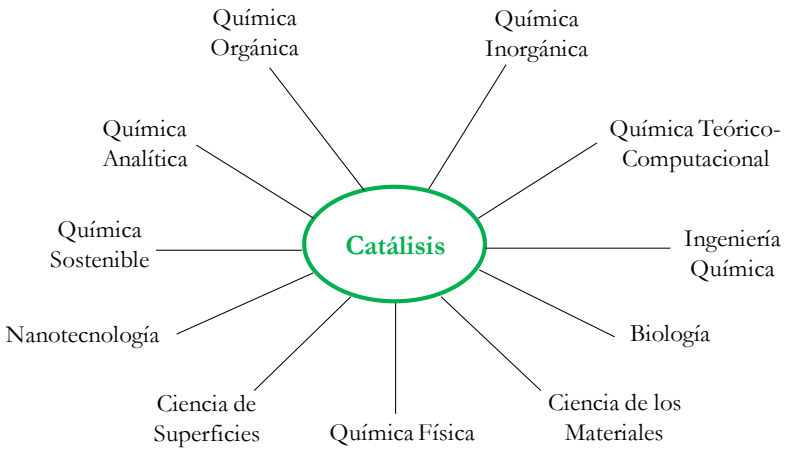


Figura 2. Disciplinas implicadas en la investigación catalítica.

Los procesos catalíticos se encuentran en la manufacturación de la mayoría de los productos químicos producidos hoy en día a nivel industrial. Históricamente, el desarrollo tecnológico de la catálisis está estrechamente relacionado con acontecimientos políticos y sociales clave, desde los primeros catalizadores a principios del siglo XX basados en metales nobles hasta la actualidad, cuando la demanda de procesos respetuosos con el medioambiente rige la evolución de esta disciplina. La catálisis heterogénea, en la que reactivos y productos se encuentran en una fase diferente a la del catalizador, habitualmente sólido, es la más utilizada tanto en la industria como a escala de laboratorio. Sin embargo, la catálisis homogénea ofrece un mayor control de la reactividad y de la selectividad y disminuye la formación de productos secundarios a la vez que facilita el estudio de los mecanismos de reacción para el posterior diseño de catalizadores mejorados.

El primer complejo de un metal de transición utilizado como catalizador fue un carbonilo de cobalto de fórmula $HCo(CO)_4$ desarrollado por Otto Roelen en 1938 para procesos de hidroformilación.[3] Más tarde, Heck y Breslow elucidaron el mecanismo de dicha reacción y, a partir de ese momento, el interés por este tipo de catalizadores fue creciendo en paralelo al desarrollo de la química organometálica. El máximo exponente de la catálisis homogénea llegó en 1965 con el descubrimiento por parte de Wilkinson del complejo $RhCl(PPh_3)_3$, conocido hoy en día como el catalizador de Wilkinson (Figura 3). Se trata de un complejo cuadrado plano capaz de hidrogenar selectivamente una gran variedad de alquenos a través de un mecanismo de adición oxidativa en presencia de hidrógeno molecular a bajas presiones.

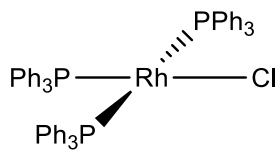
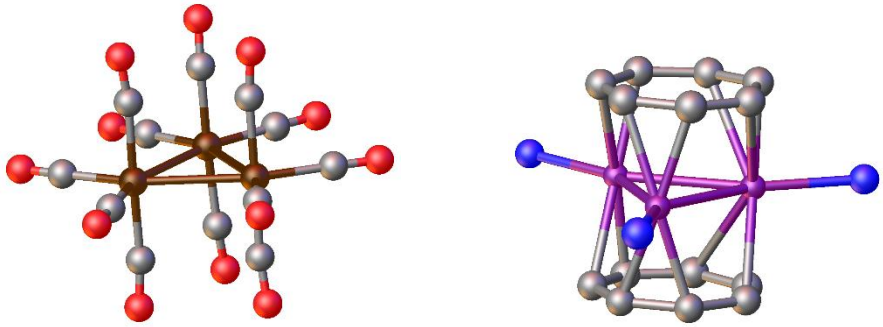


Figura 3. Representación estructural del catalizador de Wilkinson.

Los complejos organometálicos mononucleares se utilizan ampliamente en catálisis homogénea debido a su alta reactividad y selectividad. No obstante, presentan limitaciones a la hora de catalizar reacciones por etapas o que requieren efectos cooperativos entre varios átomos metálicos, tal como ocurre en las superficies metálicas de los catalizadores heterogéneos. Por su parte, los catalizadores sólidos, aunque son más fáciles de reciclar, son en general menos selectivos y resultan más difíciles de modificar con el fin de mejorar su selectividad. La catálisis homogénea basada en complejos clúster es una alternativa ya que puede combinar las ventajas de la catálisis homogénea con las de la heterogénea.[4–10] Aunque el término "clúster" se utiliza a veces de manera más amplia, en este trabajo nos restringiremos a la definición establecida por F. A. Cotton en la década de los 60, en la que dos o más átomos metálicos forman un grupo donde existen enlaces directos entre ellos.[11]

Los compuestos clúster se clasifican en función de la naturaleza del metal en clústeres de metales de los elementos principales y clústeres de metales de transición. En este trabajo nos hemos centrado en el segundo grupo, que a su vez puede dividirse en clústeres electrónicamente pobres y electrónicamente ricos. Los primeros están formados por metales situados a la izquierda de la tabla periódica en altos estados de oxidación (+2, +3 ó +4) funcionalizados con ligandos dadores de electrones tales como cloro, bromo, iodo, azufre u oxígeno. El esqueleto metálico define frecuentemente triángulos, *i.e.* $Re_3Cl_9L_3$ u octaedros *i.e.* $[Mo_6Cl_8L_6]^{4+}$ o $[Ta_6Cl_{12}L_6]^{2+}$, donde L representa un ligando dador. Los clústeres electrónicamente ricos están formados por metales situados en la parte derecha del sistema periódico y unidos a ligandos π-aceptores. La mayoría de estos compuestos son carbonilos metálicos como el complejo trinuclear $Ru_3(CO)_{12}$, pero también encontramos ejemplos de clústeres con otros ligandos con un carácter π-aceptor como son el NO o las fosfinas PR_3.

En el caso de la catálisis homogénea basada en clústeres, el mayor interés estriba en encontrar reacciones en las que la implicación de varios metales resulte en una actividad catalítica singular o superior a la observada en complejos mononucleares similares. La mayoría de ejemplos de catálisis mediada por clústeres los encontramos dentro del grupo de los electrónicamente ricos. Concretamente, una gran variedad de clústeres con ligandos carbonilo, tal como el representado en la Figura 4a, han demostrado ser excelentes pre-catalizadores o catalizadores en procesos de hidrogenación o carbonilación, entre otros. La actividad de dichos compuestos se atribuye a la facilidad de descoordinación del grupo carbonilo con la consecuente generación de intermedios con vacantes de coordinación.[4,12–14] Nordlander *et al.* han desarrollado complejos de rutenio eficientes en procesos de hidrogenación asimétrica. La enantioselectividad de la reacción les ha permitido constatar que la integridad del clúster se mantiene durante el proceso.[15,16] Recientemente, Yadong Li *et al.* han descrito la eficacia de un clúster de unidad Pd_3, representado en la Figura 4b, en la reacción de cicloisomerización de aminas. En este último trabajo, diversas técnicas *in situ* les permiten demostrar que el complejo trinuclear es la especie activa.[17]



(a) (b)

Figura 4. Estructuras de los complejos $Ru_3(CO)_{12}$ (a) y $[Pd_3(C_7H_7)_2(MeCN)_3]^{2+}$ (b).

La presencia de distintos metales en un mismo clúster resulta en efectos cooperativos que magnifican la actividad de estos complejos heterobimetálicos. Ejemplos de ello son los clústeres de fórmula $[Pt(AuL)_8]^{2+}$ cuya actividad catalítica es mayor que la de los complejos de platino homometálicos en procesos de intercambio entre H_2 y D_2.[18] De manera similar, el clúster $[Pt_3Ru_6H_2(CO)_{20}(PhCCPh)]$ es un buen catalizador para la hidrogenación del alquino PhCCPh.[19] El mayor reto en este tipo de catálisis consiste en entender la acción de los diferentes metales en cada reacción catalítica para, de esta forma, diseñar nuevos clústeres con propiedades óptimas.

Muchos de los clústeres clasificados como electrónicamente pobres se han desarrollado con el fin de mimetizar los centros activos de las enzimas y de los catalizadores sólidos más ampliamente utilizados en la industria. La nitrogenasa convierte el nitrógeno atmosférico en amoniaco y es la responsable de suministrar nitrógeno a los organismos vivos. Esta enzima contiene dos componentes: una proteína de hierro y una proteína de molibdeno y hierro. La primera es la responsable de proporcionar electrones y la segunda contiene el centro activo de la enzima, denominado cofactor Fe-Mo y que presenta una subunidad $MoFe_3S_4$ en su estructura.[20,21] En la figura 5 se muestran algunos de los clústeres que se han sintetizado con el fin de imitar los centros activos de esta enzima tan importante en la naturaleza.[21,22]

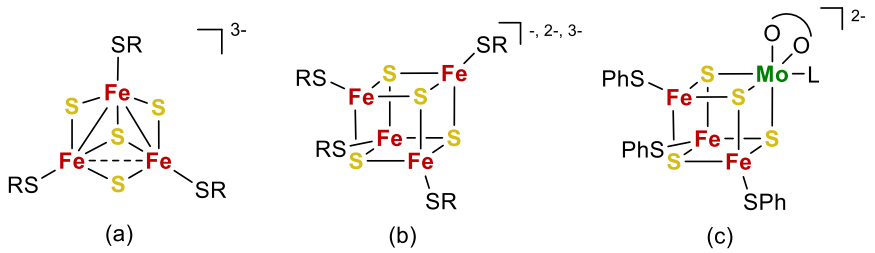


Figura 5. Complejos clúster que mimetizan centros activos de proteínas. R = metil, etil, fenil o grupos relacionados; L = ligandos dadores de 2 electrones; O⌒O= catecolato.

El disulfuro de molibdeno se utiliza en la industria petroquímica como catalizador en procesos de hidrotratamiento para eliminar azufre, nitrógeno y oxígeno de las materias primas de origen fósil. El MoS_2 presenta una estructura laminar en la que las diferentes capas interaccionan entre sí mediante fuerzas de Van der Waals. Cada una de estas láminas está constituida por tres capas, una central de átomos de molibdeno y dos de azufre, donde los átomos metálicos están dispuestos formando triángulos y enlazados covalentemente mediante azufres puente. La profesora Dubois y colaboradores han desarrollado una serie de complejos, representados en las Figuras 6a y 6b, que comparten características estructurales con este catalizador sólido, ya que poseen átomos de molibdeno unidos por azufres puente.[23] Por otra parte, existe una extensa familia de clústeres trinucleares Mo_3S_4 con unidad de cubo incompleto que también guardan una estrecha relación topológica con dicho catalizador (Figura 6c). Tanto en las dos estructuras dinucleares como en la gran mayoría de los clústeres con unidad Mo_3S_4, el estado de oxidación del molibdeno es +4 que coincide con el del sólido MoS_2.

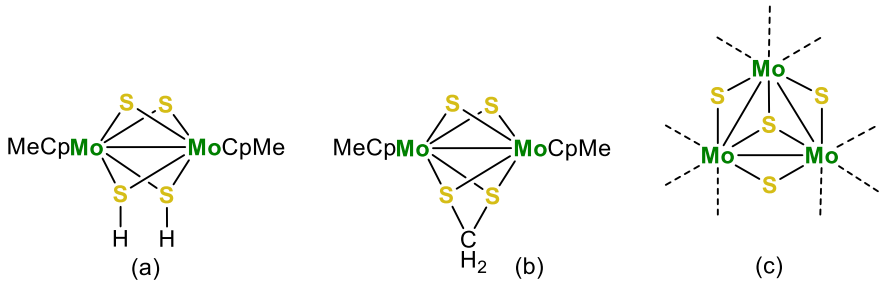


Figura 6. Representación estructural de clústeres di- y trinucleares de molibdeno y azufre.

Los complejos dinucleares representados en las Figuras 6a y 6b catalizan de manera eficiente la hidrogenación de sustratos orgánicos tales como nitroarenos, azidas, azocompuestos, iminas, isocianatos e isotiocianatos.[23] En relación a los clústeres sulfuro de molibdeno con estructura cuboidal, los primeros estudios acerca de su actividad catalítica se centraron en los clústeres heterobimetálicos que resultan al

incorporar un heterometal a la unidad trimetálica, tal como se representa en la Figura 7. Así, los clústeres Mo_3S_4 actúan como metaloligandos frente a un segundo metal M', generalmente un metal de transición, para formar compuestos de unidad $Mo_3M'S_4$. Esta estrategia de síntesis se conoce con el nombre de construcción por bloques [3+1] y fue descrita por Shibahara y colaboradores en el año 1986, cuando hicieron reaccionar hierro metal con el clúster $[Mo_3S_4(H_2O)_9]^+$ para dar lugar al complejo $[Mo_3Fe(H_2O)S_4(H_2O)_9]^+$.[24]

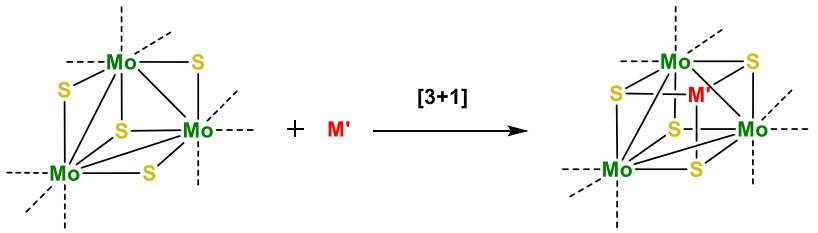


Figura 7. Estrategia de síntesis para la obtención de clústeres $Mo_3M'S_4$.

En general, la actividad catalítica de estos clústeres $Mo_3M'S_4$ recae sobre el heterometal M'. Por ejemplo, los clústeres Mo_3PdS_4 son catalizadores activos en reacciones de adición de alcoholes, aminas primarias y ácidos carboxílicos a alquinos,[25] y sus homólogos con unidad Mo_3NiS_4, además de catalizar esta última adición intramolecular para dar lugar a enol lactonas,[26] también se usan en la catálisis de hidrodesulfuración.[27–29] Los clústeres de unidad Mo_3RuS_4 son activos en la polimerización de metilmetacrilato y en la descomposición de hidracina para dar lugar a amoniaco y nitrógeno,[21,30] mientras que los complejos ópticamente puros con unidad Mo_3CuS_4 catalizan la ciclopropanación de α-olefinas.[31,32]

Las primeras evidencias acerca de la actividad catalítica de los clústeres Mo_3S_4 se publican entrado ya el siglo XXI y surgen a partir de investigaciones sobre la evolución fotocatalítica de hidrógeno a partir de agua. Los clústeres de fórmula $[Mo_3S_4(\eta_5\text{-Cp'})_3]^+$ o $[Mo_3S_4(H_2O)_9]^{4+}$ absorbidos sobre sólidos semiconductores, tales

como sílice dopada de tipo p o perovskitas $NaTiO_3$, catalizan eficientemente la reducción de los protones del agua.[33–35] Posteriormente, en el grupo de la Profesora Rosa Llusar donde se ha realizado este trabajo de tesis doctoral, se demuestra la eficacia de estos sistemas en procesos catalíticos homogéneos dirigidos a la obtención de productos de elevado valor añadido en la industria. Concretamente, los clústeres hidruro de fórmula $[Mo_3S_4H_3(difosfina)_3]^+$ se aplican como catalizadores en la reacción de hidrodefluoración de la pentafluoropiridina.[36,37] A continuación, en colaboración con el grupo del Profesor Matthias Beller, se demuestra su actividad catalítica en la reducción selectiva de nitroarenos a anilinas.[38] Estudios más recientes muestran que los clústeres Mo_3S_4 derivados con aminofosfinas catalizan procesos de reducción de cetonas a alcoholes.[39]

La unidad clúster Mo_3S_4 es una entidad robusta debido a la presencia de azufres puente y por lo tanto susceptible de ser funcionalizada con una gran variedad de ligandos. El clúster de fórmula $[Mo_3S_4Cp_3]^+$ (Cp = ciclopentadienilo) descrito por Dahl y colaboradores a principios de los años 70 representa el primer ejemplo con esta unidad cuboidal.[40] Aunque este complejo contiene ligandos de naturaleza π-dadora, a partir de los años 80 se desarrolló una extensa familia de clústeres Mo_3S_4 funcionalizados con ligandos σ-dadores. Entre ellos se encuentra el grupo de ligandos monodentados como el H_2O, el NH_3, el formiato y los ligandos haluro y pseudohaluro, así como diversos ligandos bi- y tridentados dadores de oxígeno y/o nitrógeno tales como el oxalato, el acetilacetonato, el iminodiacetato o el nitrilotriacetato. Por otra parte, existe una importante variedad de mono- y difosfinas que se han coordinado a la unidad clúster Mo_3S_4.[41] Cabe destacar la obtención de clústeres hidruro funcionalizados con ligandos difosfina y su papel en catálisis orgánica, tal y como se ha mencionado en el párrafo anterior.

Tras explorar la actividad catalítica de los complejos difosfino y aminofosfino de unidad Mo_3S_4, la presente tesis plantea una extensión de esta química a complejos

diamino y diimino. El potencial del grupo NH presente en los complejos diamino para participar activamente en procesos catalíticos ha impulsado el uso de este tipo de ligandos.[42] Se trata de un grupo clave para la obtención de catalizadores multifuncionales, en los que existe una cooperación metal-ligando, capaces de mimetizar la actividad de las enzimas en las transformaciones químicas. Por otra parte, los ligandos diimino, tales como la bipiridina o la fenantrolina, presentan propiedades ópticas y fotoquímicas muy interesantes. En consecuencia, los complejos de metales de transición con ligandos de esta naturaleza se utilizan como materiales activos en fotocatálisis.[43]

De entre todos los procesos catalíticos, aquéllos dirigidos a la producción de aminas son especialmente relevantes ya que éstas se utilizan en la preparación de una gran variedad de compuestos nitrogenados biológicamente activos, productos agroquímicos, pigmentos, polímeros y medicamentos.[44–46] Actualmente, la obtención de aminas bajo condiciones más respetuosas con el medioambiente constituye todo un reto tanto en la industria como a escala de laboratorio, así como la búsqueda de catalizadores más económicos que no estén basados en metales nobles. La metodología de preparación más común para la obtención de anilinas conlleva una reacción de nitración de un areno, seguida por la reducción del grupo nitro. Por ello, esta última transformación es de suma importancia en la actualidad.[47]

En la búsqueda de procesos que sean respetuosos con el medioambiente, la catálisis en tándem es una alternativa que permite obtener productos complejos y de gran valor industrial o farmacéutico a partir de materiales relativamente simples mediante procesos eficientes sin necesidad de aislar los intermedios. Estas transformaciones constituyen hoy en día un importante campo de investigación, puesto que presentan ventajas tanto económicas como medioambientales. Por este motivo, dos de los trabajos que se incluyen en la presente tesis doctoral están dirigidos a la obtención de aminas mediante procesos de catálisis tándem. Si continuamos con

la investigación de procesos más "verdes" para la reducción de nitrocompuestos, la utilización de hidrógeno molecular representa uno de los pilares fundamentales en la industria química,[48–51] pues se estima que aproximadamente el 25% de todos los procesos químicos incluyen al menos un paso de hidrogenación catalítica.[52,53]

El trabajo de investigación que aquí se presenta, se ha centrado en el estudio de la actividad catalítica de sulfuros clúster de molibdeno funcionalizados con ligandos *N,N'*-dadores, en concreto, diaminas y ligandos derivados de la bipiridina. Dicho trabajo se ha dirigido hacia la obtención de aminas primarias, secundarias y terciarias mediante procesos de reducción económicos y/o de bajo impacto medioambiental. Uno de los mayores retos en el ámbito de la catálisis de reducción es encontrar procesos altamente selectivos. Por esta razón, la quimioselectividad de los catalizadores utilizados en todos los procesos estudiados en esta tesis se ha evaluado extensamente. Por otro lado, la catálisis mediada por clústeres requiere que ésta tenga lugar sin la fragmentación de los mismos. Con el fin de demostrar la integridad de la unidad clúster, hemos combinado una variedad de técnicas experimentales, algunas de ellas *in situ*. Además, dichas técnicas se han utilizado para obtener información acerca de los mecanismos de reacción que sirva de apoyo a futuros estudios teórico-mecanísticos.

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2

Objetivos

2. Objetivos

"No puedo cambiar la dirección del viento, pero puedo ajustar mis velas para alcanzar mi destino."

Jimmi Dean

Las aminas son productos muy valiosos tanto a nivel industrial como a escala de laboratorio por tratarse de intermedios en la preparación de medicamentos, pigmentos y productos químicos para la agricultura, entre otros. La presente tesis doctoral se centra en el desarrollo de catalizadores que permitan obtener aminas mediante procesos sostenibles. En este sentido, los sulfuros clúster con unidad Mo_3S_4 se presentan como una alternativa a los metales nobles como catalizadores para la síntesis de estos intermedios. La robustez de esta entidad trimetálica permite la modificación de su entorno de coordinación con el fin de conferirle unas determinadas propiedades. Este trabajo, no sólo se ha centrado en la búsqueda de nuevos catalizadores, sino también en el desarrollo de protocolos selectivos de bajo impacto medioambiental que permitan la obtención de aminas a partir de materiales económicos. Los objetivos concretos de esta tesis son los siguientes:

i. Funcionalización química de la unidad Mo_3S_4 con ligandos diamina y diimina, optimización de las estrategias de síntesis de estos complejos y caracterización estructural.
ii. Síntesis de clústeres heterobimetálicos con unidad Mo_3PtS_4, caracterización estructural y estudio de sus propiedades electroquímicas.
iii. Estudio de la actividad catalítica de los clústeres trinucleares en la síntesis quimioselectiva de aminas primarias.
iv. Desarrollo de procesos tándem catalizados por los clústeres tri- y tetrametálicos para la preparación de aminas secundarias y terciarias.

3

A mild and chemoselective reduction of nitro and azo compounds catalyzed by a well-defined Mo_3S_4 cluster bearing diamine ligands

3. A mild and chemoselective reduction of nitro and azo compounds catalyzed by a well-defined Mo_3S_4 cluster bearing diamine ligands.
   3.1. Manuscript
   3.2. Supporting Information

"Un científico en su laboratorio no es sólo un técnico: es también un niño situado ante fenómenos naturales que le impresionan como un cuento de hadas."

Marie Curie

A Mild and Chemoselective Reduction of Nitro and Azo Compounds Catalyzed by a Well-defined Mo_3S_4 Cluster Bearing Diamine Ligands

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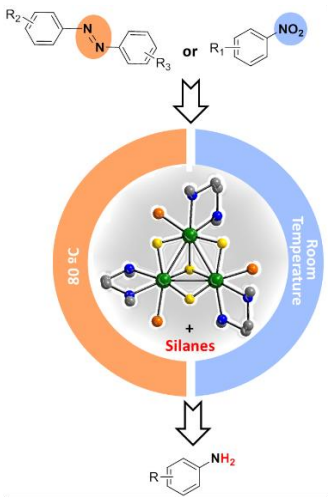


Reduction made easy: A novel cubane-type $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (dmen: N,N'-dimethylethylenediamine) molecular cluster has been established as a potential chemoselective catalyst for the facile reduction of nitroarenes and azo compounds to anilines under mild conditions with silanes as reducing agents.

Abstract

Herein, we report a novel well-defined diamino Mo_3S_4-based catalyst system for the reduction of nitroarenes and azo compounds to the corresponding anilines using silanes as reducing agents. This catalytic protocol provides a facile route to access aromatic amines under mild conditions in good to excellent yields. Notably, even anilines functionalized with other potentially reducible moieties are obtained with high selectivity. The new chemoselective catalyst of formula $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (dmen = *N*,*N*′-dimethylethylenediamine), is conveniently synthesized through coordination of the diamine ligand to the incomplete Mo_3S_4 cubane-type cluster core in a one pot two-step procedure. The crystal structure of the $[Mo_3S_4Cl_3(dmen)_3]^+$ cation confirms the formation of a single isomer in which the chlorine atom lies *trans* to the bridging sulfur atom to afford a C_3 symmetry complex with intrinsic backbone chirality. The structure is preserved in solution as evidenced by multinuclear NMR spectroscopy and electrospray-ionization mass spectrometric techniques.

Introduction

Aromatic amines are important intermediates in the manufacture of dyes, pigments, agrochemicals, pharmaceuticals and polymers.[1] The most common approach for their preparation is based on reduction processes with nitroarenes or, less frequently, the corresponding azo compounds as starting materials.[2,3] Among the well-established reduction methods, catalytic hydrogenation in the presence of heterogeneous catalysts is preferred for industrial-scale production. However, despite the significant progress achieved during the last decades, this methodology still has limitations with regard to substrates functionalized with other reducible groups.[4] Consequently, for the synthesis of structurally complex amines decorated with diverse functional groups nowadays, the use of selective homogeneous catalysts is still the most selective approach. Typically, the catalytic reduction of nitroarenes is performed at comparably high temperature and high pressure with flammable

molecular hydrogen. Hence, especially on the laboratory scale, the development of safe, efficient, and chemoselective catalytic reduction routes for the synthesis of anilines that can be performed under milder conditions (room temperature and atmospheric pressure) is of continuing interest. In this respect, catalytic hydrosilylation is a suitable tool for the reduction of nitro and azo compounds. Interestingly, so far, a general protocol for the reductive cleavage of azo compounds under hydrosilylation conditions remains elusive, and only a few homogeneous catalysts are available for the reduction of the nitro functionality.[5]

Recently, we have shown the selective transfer hydrogenation of aromatic nitro compounds catalyzed by a cubane-type Mo_3S_4 cluster functionalized with outer diphosphane ligands,[6] which was also active for the partial hydrodefluorination of pentafluoropyridine.[7] As a continuation of our research program focused on the preparation of well-defined cluster catalysts, we became interested in the novel functionalization of the Mo_3S_4 cluster core with diamine ligands instead of the expensive and easily oxidizable diphosphanes.[8] Herein, we report for the first time the synthesis and structure of the cubane-type $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (dmen = *N*,*N*′-dimethylethylenediamine) cluster and its use as a catalyst for the selective hydrosilylation of a variety of aromatic nitro and azo compounds to give the corresponding anilines under mild conditions. To the best of our knowledge there is only one previous example on molybdenum catalyzed hydrosilylation of this kind of substrate. More specifically, Fernandes and Romao found, during their investigations on the hydrosilylation of esters, that the nitro group of methyl 4-nitrobenzoate was selectively reduced with $PhSiH_3$ by using MoO_2Cl_2 as a catalyst under harsh conditions.[5e]

Results and Discussion

Synthesis and characterization of the catalyst

Polymeric $\{Mo_3(\mu_3\text{-}S)(\mu\text{-}S_2)_3X_4\}_n$ or molecular $[Mo_3(\mu_3\text{-}S)(\mu\text{-}S_2)_3X_6]^{2-}$ (X=Cl or Br) compounds are the chosen precursors to access the chemistry of cuboidal Mo_3S_4 cluster complexes containing diphosphane ligands. Remarkably, the resulting trinuclear complexes are isolated in high yields as single isomers with C_3 symmetry and instrinsic chirality, as shown in Figure 1. The driving force for the conversion of the $Mo_3(\mu_3\text{-}S)(\mu\text{-}S_2)_3$ unit into the incomplete cubane-type $Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3$ cluster core is the reduction of the disulfide bridges to sulfide groups by the phosphane groups, which limits the field of application. In consequence, other synthetic strategies have been employed to functionalize the Mo_3S_4 cluster core with non-phosphorus-based chelate ligands.

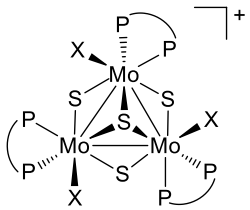
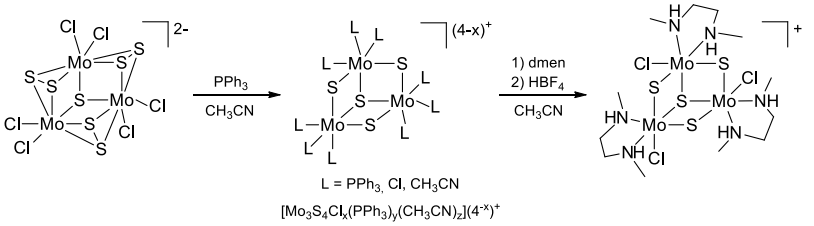


Figure 1. Cubane-type diphosphane Mo_3S_4 cluster.

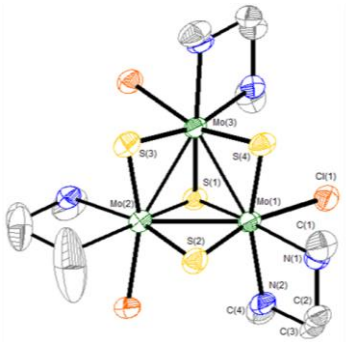
Substitution of the outer water molecules in the $[Mo_3S_4(H_2O)_9]^{4+}$ aqua complex, which is only stable in strongly acidic solutions, allows for the formation of a large number of derivatives including two triamine complexes.[9] However, the competitive protonation of the amino ligands results in low to moderate reaction yields. To overcome this limitation, we and others designed an expanded two-step version of this approach by replacing the water molecules by thiourea ligands to afford the $[Mo_3S_4(tu)_8(H_2O)]^{4+}$ cluster cation, which is isolated as its chloride salt. The high lability of the thiourea ligands has been used to prepare trisubstituted diimino Mo_3S_4 complexes bearing 2,2'-bipyridine and 1,10-phenanthroline ligands.[10]

Alternatively, $[Mo_3(\mu_3\text{-}S)(\mu\text{-}S_2)_3X_6]^{2-}$ has been employed, upon treatment with triphenylphosphine, to generate in-situ "$[Mo_3S_4Cl_x(PPh_3)_y(solvent)_z]^{(4-x)+}$" species in order to avoid the laborious procedure involving the use of the $[Mo_3S_4(H_2O)_9]^{4+}$ aqua ion as the precursor.[11] Ligand exchange at the preformed Mo_3S_4 cluster unit has been used successfully to prepare several Mo_3S_4 complexes containing diphosphanes decorated with tetrathiofulvalene or hydroxyalkyl functional groups, for which no suitable direct synthesis starting from Mo_3S_7 compounds could be found.[12, 13] In this work, we have explored the substitution of the outer ligands in "$[Mo_3S_4Cl_x(PPh_3)_y(solv)_z]^{(4-x)+}$" by *N,N′*-dimethylethylenediamine (dmen) with CH_3CN as the solvent under slightly acidic conditions (Scheme 1). Such conditions are required to prevent the partial substitution of the chlorine terminal ligands by hydroxo groups generated from adventitious water molecules.



Scheme 1. Synthetic route for the preparation of $[Mo_3S_4Cl_3(dmen)_3]^+$.

The desired $[Mo_3S_4Cl_3(dmen)_3]BF_4$ product was isolated in 75 % as an air-stable green solid and was crystallized by slow evaporation from dichloromethane:diethyl eter solutions. The molecular structure of the $[Mo_3S_4Cl_3(dmen)_3]^+$ cation is shown in Figure 2, together with a list of selected bond lengths. Remarkably, only one of all possible isomers is formed, a situation already encountered in the chemistry of the analogous diphosphane or aminophosphane M_3S_4 (M = Mo, W) derivatives.[14]



Averaged bond distances[a]

Mo-Mo	2.759[3]
Mo-(μ_3-S)	2.335[4]
Mo-(μ-S)[b]	2.301[5]
Mo-(μ-S)[c]	2.288[7]
Mo-N[d]	2.278[6]
Mo-N[e]	2.298[18]
Mo-Cl	2.492[14]

Figure 2. Selected bond lengths and ORTEP representation (50% probability ellipsoids) of the cationic $[Mo_3S_4Cl_3(dmen)_3]^+$ complex, in which hydrogen atoms have been omitted for clarity. [a] Standard deviations for average values are given in square brackets. [b] Mo-(μ-S) length *trans* to the Mo-N bond. [c] Mo-(μ-S) length *trans* to the Mo-Cl bond. [d] Length *trans* to the Mo-(μ_3-S) bond. [e] Length *cis* to the Mo-(μ_3-S) bond.

The structure consists of an incomplete cubane-type arrangement in which the molybdenum and sulfur atoms occupy adjacent vertices with a missing metal position. In general, the metal-metal and metal-sulfur distances within the Mo_3S_4 cluster core follow the same tendencies observed for other trinuclear Mo_3S_4 species.[10,15] Each molybdenum atom presents a pseudooctahedral coordination environment with three sulfur, one chlorine and two nitrogen atoms. Remarkably, the diamine ligand is coordinated asymmetrically to the metal cluster core with one nitrogen atom attached *trans* and the other one *cis* to the capping sulfur atom (μ_3-S). This specific arrangement leads to a C_3 symmetry cluster furnished with inherent backbone chirality. In this case, the $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ complex was obtained as a racemic mixture because of the absence of an optically pure source, such as chiral counterions or chiral ligands.[15b, 16]

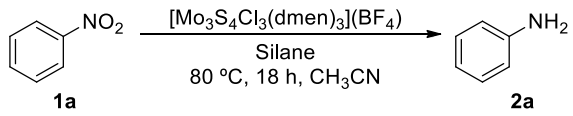
The structural integrity of the cluster in solution was proved by multinuclear NMR spectroscopy and electrospray-ionization (ESI) mass spectrometry. In accordance with the C_3 symmetry of the complex, the ^{13}C NMR spectrum reveals four singlets corresponding to the methyl and ethylene bridged groups of the

diamines (Figure SI1 in the Supporting Information). In the ^{1}H NMR spectrum, the two main signals correspond to the two methyl groups. Both signals appear as doublets ($^{2}J_{H\text{-}H(N)}$ = 5.6 and 5.9 Hz) as a result of coupling with the proton attached to the nitrogen atom (Figure SI2 in the Supporting Information). However, ^{1}H-^{13}C gradient HSQC correlation experiments were required for the complete signal assignment. In particular, this multinuclear experiment was useful to discriminate between the protons of the amino groups (N-H) and the diastereotopic protons of the ethylene bridged groups, which appear partially overlapped with one of the methyl groups too (Figure SI3 in the Supporting Information). The positive ESI mass spectrum shows one peak centered at m/z = 786.6, which is associated to the pseudomolecular $[Mo_3S_4Cl_3(dmen)_3]^+$ ion on the basis of the m/z value and its characteristic isotopic pattern (Figure SI4 in the Supporting Information).

Catalytic performance

At the start of our catalytic studies, the hydrosilylation of nitrobenzene (**1a**) in the presence of the previously described $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ complex was investigated as a benchmark system for the optimization of the conditions. The effects of the hydrogen source, solvent, catalyst loading, and reaction temperature were evaluated (see also the Supporting Information). Initially, the hydrosilylation reaction was carried out at T = 80 ºC with different alkyl, aryl, and alkoxy silanes, as well as polymethylhydrosiloxane (PMHS). To our delight, full conversion with an excellent yield of aniline (**2a**) was achieved by applying diphenylsilane or phenylsilane as the reductant (Table 1, entries 4 and 5). In contrast to the reactivity of the previously reported cubane-type Mo_3S_4 cluster functionalized with diphosphane ligands, the reduction of **1a** under transfer hydrogenation conditions with formic acid or formates led to much lower conversion and yield (Table SI1 in the Supporting Information). Notably, no reaction took place in the absence of reducing agent and/or catalyst.

Table 1. Mo_3S_4-catalyzed hydrosilylation of nitrobenzene (**1a**).[a]



Entry	Reducing agent	Conversion [%][b]	Yield [%][b]
1	Et_3SiH	65	64
2	Me_2PhSiH	82	82
3	Ph_3SiH	1	1
4	Ph_2SiH_2	>99	94
5	$PhSiH_3$	>99	90
6	$Me(EtO)_2SiH$	46	46
7	$(EtO)_3SiH$	2	2
8	PMHS	19	19
9[c]	Ph_2SiH_2	>99	>99

[a] Reaction conditions: **1a** (0.1 mmol), silane (3.5 equiv.), catalyst (5 mol%), CH_3CN (2 mL). [b] Determined by GC with anisole as an internal standard. [c] CH_3OH (2 mL) as solvent; t = 2 h at T = 80 ºC or 18 h at RT.

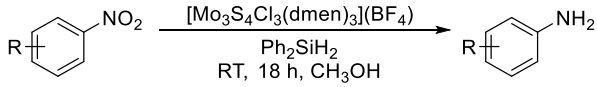
Next, the effect of different solvents was studied (Table SI2 in the Supporting Information). We were grateful that a quantitative yield of **2a** was achieved in MeOH (Table 1, entry 9). In other tested polar solvents, such as CH_3CN, THF and EtOH, an excellent yield of **2a** was also afforded, whereas the use of isopropanol led to a slightly lower reactivity. Finally, a gradual decrease of the temperature revealed that the desired catalytic reaction can be carried out at room temperature without any loss of reactivity (Table 1, entry 9). Under these conditions, the accumulation of the

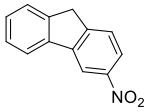
carcinogenic and potentially explosive hydroxylamines is a common drawback because they are often less reactive than the corresponding starting nitroarenes.[17] Interestingly, in the presence of our Mo_3S_4 cluster catalyst, no traces (<1%) of *N*-phenylhydroxylamine (**3a**) were detected.

Next, the scope of this catalyst system was studied in detail by testing a variety of structurally diverse nitro compounds (Table 2). In general, nitroarenes bearing either electron-donating or electron-withdrawing groups located in different ring positions were smoothly reduced at room temperature to afford the corresponding anilines in good to excellent yields. For example, simple alkyl-substituted nitroarenes and 4-nitrobenzotrifluoride are equally well reduced into the corresponding anilines (Table 2, entries 1-3). Interestingly, the reduction of a series of halide-containing nitroarenes proceeded without the formation of any dehalogenation products and halogen-substituted anilines were obtained in excellent yields (Table 2, entries 4-9). Moreover, 1,4-diaminobenzene and 3-aminobenzyl alcohol are easily accessible from the corresponding nitroarenes in 92 and 86% yield, respectively (Table 2, entries 10 and 11). Notably, the reduction of bulkier molecules, such as 2-nitrofluorene, was also successfully carried out at higher temperatures to afford the corresponding aniline in 88% yield (Table 2, entry 12).

We then became interested in the preparation of more demanding anilines functionalized with other reducible groups located in different ring positions. To our delight, the Mo_3S_4 cluster catalyst is also able to reduce with good selectivity the nitro group in substrates bearing cyanide, ketone, ester, and even C-C double bond functionalities (Table 2, entries 13-19).

Table 2. Mo_3S_4-catalyzed hydrosilylation of functionalized nitroarenes.[a]



Entry	Nitroarene	Conversion [%][b]	Yield [%][b]
1	R: 3-Me	>99	93 (81)
2[c]	R: 4-*t*Bu	>99	>99 (90)
3	R: 4-CF_3	>99	97
4	R: 4-F	>99	>99 (85)
5[d]	R: 4-Cl	>99	>99
6	R: 3-Cl	>99	94 (85)
7	R: 2-Cl	>99	>99
8[c]	R: 4-Br	>99	>99 (90)
9[c, e]	R: 4-I	>99	92
10	R: 4-NH_2	>99	92
11	R: 3-CH_2OH	99	86
12[c, d]		>99	88
13	R: 4-CN	>99	73
14	R: 2-CN	>99	62
15[c]	R: 4-COMe	>99	83

Entry	Nitroarene	Conversion [%][b]	Yield [%][b]
16	R: 2-COMe	>99	75
17[c,e]	R: 4-CO_2Me	>99	>99 (88)
18	R: 2-CO_2Me	>99	92
19[c,e]	R: 3-$CHCH_2$	>99	83

[a] Reaction conditions: nitroarene (0.1 mmol), Ph_2SiH_2 (3.5 equiv.), catalyst (5 mol%), CH_3OH (2 mL). [b] Determined by GC with anisole as an internal standard; yields of isolated products given in parentheses. [c] Catalyst (6 mol%). [d] T = 80 ºC [e] Ph_2SiH_2 (5 equiv.).

With respect to the reaction mechanism, it is generally accepted that the reduction of nitroarenes to anilines can proceed through two different routes: 1) direct reduction via the nitrosoarene and the hydroxylamine derivates and 2) a condensation reaction of these intermediates to produce the corresponding azoxyarenes, followed by in situ reduction through the formation of the azo and hydrazo derivates.[18] To gain further insights into the preferred pathway followed in the presence of our Mo_3S_4 cluster catalyst, some known intermediates, namely *N*-phenylhydroxylamine (**3a**), nitrosobenzene (**4a**), azoxybenzene (**5a**), and azobenzene (**6a**), were subjected to our reduction protocol (Table 3). These experiments were carried out with a higher catalyst loading (20 mol%) because the transient nature of these intermediates during the reaction from nitrobenzene (**1a**) makes the relative amount of catalyst much higher than the normal catalytic amount. Whereas the reduction of **3a** and **4a** gave aniline (**2a**) in 92 and 86% yields, respectively, **5a** was only partially converted to afford **2a** in 32% yield (Table 3, entries 1-3). These results clearly suggest that the condensation pathway is disfavored, and therefore, the formation of aniline (**2a**) proceeds preferentially through the direct reduction route.

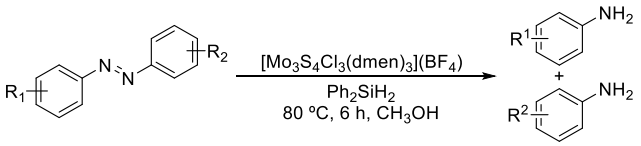
Table 3. Reduction of possible reaction intermediates for the hydrosilylation of nitrobenze (**1a**).[a]

Entry	Substrate	Conversion [%][b]	Yield [%][b]
1	Ph-NHOH (**3a**)	>99	92
2	Ph-NO (**4a**)	>99	86
3	Ph-NO=N-Ph (**5a**)	39	32
4	Ph-N=N-Ph (**6a**)	97	94

[a] Reaction conditions: substrate (0.1 mmol), Ph_2SiH_2 (3.5 equiv.), catalyst (20 mol%), CH_3OH (2 mL), t = 2 h, T = 80 ºC. [b] Determined by GC with anisole as an internal standard.

Interestingly, when azobenzene (**6a**) was treated under otherwise the same reaction conditions almost full conversion with a 94% yield of aniline (**2a**) was achieved (Table 3, entry 4). After study of this reduction reaction in more detail, an optimal result with a quantitative yield of **2a** was obtained after t = 6h at T = 80 ºC with 5 mol% and 4.5 equivalents of catalyst loading and diphenylsilane, respectively. Encouraged by this result, we explored the feasibility of this protocol for the hydrosilylation of other azo compounds (Table 4). Relative to the nitro reduction, the cleavage of the azo functionality in the presence of our Mo_3S_4 cluster catalyst is less effective. However, as in the case of **6a**, by increasing the silane and/or catalyst loading, the cleavage of asymmetrical alkyl- and/or amine- functionalized azoarenes was successfully accomplished at T = 80 ºC to afford the corresponding anilines in up to 99% yield.

Table 4. Mo_3S_4-catalyzed hydrosilylation of azo compounds.[a]



Entry	Azoarene		Conversion [%][b]	Yield [%][b]	
	R_1	R_2		R_1	R_2
1	H	H	>99	>99	
2[c]	H	Me	>99	>99	>99
3[c]	H	NH_2	>99	>99	80
4	H	$N(Me)_2$	>99	96	89
5[c]	Me	$N(Me)_2$	>99	98	97
6[c]	$N(Me)_2$	NH_2	>99	91	>99

[a] Reaction conditions: azoarene (0.1 mmol), Ph_2SiH_2 (4.5 equiv.), catalyst (5 mol%), CH_3OH (2 mL). [b] Determined by GC with anisole as an internal standard. [c] Ph_2SiH_2 (5.5 equiv.), catalyst (6 mol%).

Finally, to get clues about the cluster integrity during catalysis, the reduction of **1a** was monitored by ESI mass spectrometry with a pressurized sample infusion method.[19] Remarkably, this technique allowed us to unravel valuable mechanistic information for the previously reported Mo_3S_4-catalyzed transfer hydrogenation of nitroarenes and to demonstrate that cluster catalysis could be unequivocally invoked.[6] Monitoring of the **1a** catalytic reduction (see Figure SI5 in the Supporting Information) revealed that catalysis occurs without degradation of the $[Mo_3S_4Cl_3(dmen)_3]^+$ cluster catalyst and prompted us to assume that the hypothetical hydrido species (Mo-H) generated by silane activation are formed without cleavage of the Mo-Cl bond, as found in the analogous cubane-type Mo_3S_4 clusters functionalized with outer diphosphane ligands.[6,11a,15b] Furthermore, an additional

control experiment was carried out with hydrogen (1 atm) instead of Ph_2SiH_2 as the reducing agent. Interestingly, no conversion of **1a** was achieved, which thus precluded a possible direct hydrogenation by hydrogen generated from reaction of the silane with methanol. Although this result supports the idea that catalysis proceeds via the formation of molybdenum hydrido species (Mo-H), our efforts to capture the silylmolybdenum cluster intermediates in the actual catalytic system have been unsuccessful, and therefore, the intimate mechanism of formation of these intermediates and the subsequent reactivity is not entirely clear.

Conclusions

In summary, we have developed a new and efficient protocol for the preparation of structurally diverse anilines by reduction of the corresponding nitro or azo compounds. For both substrates, the reactions proceed easily under mild conditions (room temperature or T = 80 ºC, ambient pressure) with silanes as the reducing agents. This catalytic protocol shows good functional-group tolerance towards other easily reducible moieties, such as vinyl, acetyl, cyanide or ester groups. As the catalyst, a well-defined Mo_3S_4 complex bearing diamine ligands has been employed. The preparation of this novel catalyst, namely $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (dmen: *N,N'*-dimethylethylenediamine), has been carried out by the unprecedented coordination of diamine ligands to the Mo_3S_4 cluster core in a one-pot two-step procedure from the readily available $[Mo_3S_7Cl_6]^{2-}$ dianion. The molecular structure of this complex has been determined by multinuclear NMR spectroscopy, electrospray-ionization mass spectrometry, and single-crystal X-ray crystallography.

Experimental Section

General remarks

All reactions were performed under a nitrogen atmosphere with standard Schlenck techniques. The molecular complex $(n\text{Bu}_4\text{N})_2[\text{Mo}_3\text{S}_7\text{Cl}_6]$ was prepared according to the literature procedure.[11d]

Physical measurements

Elemental analyses were carried out on a EuroEA3000 Eurovector Analyzer. Electrospray-ionization mass spectra were recorded with a Quattro LC (quadrupole-hexapole-quadrupole) mass spectrometer with an orthogonal Z-spray electrospray interface (Micromass, Manchester, UK). The cone voltage was set at 20 V unless otherwise stated, with CH_3CN as the mobile phase solvent. Sample solutions were infused through a syringe pump directly connected to the ESI source at a flow rate of 10 $\mu Lmin^{-1}$, and a capillary voltage of 3.5 kV was used in the positive scan mode. Nitrogen was employed as the drying and nebulizing gas. Isotope experimental patterns were compared with theoretical patterns obtained by using the MassLynx 4.1 program.[20] ^1H and ^{13}C NMR spectra were recorded on a Varian Innova 300 MHz spectrometer with CD_2Cl_2 as the solvent. ^1H-^{13}C gradient HSQC spectra were recorded on a Varian Innova 500 MHz spectrometer with CD_2Cl_2 as a the solvent. Gas chromatography analyses were performed on an Agilent 7820 A GC system equipped with a flame ionization detector and a capillary column (Agilent HP-5, 30 m x 0.32mm x 0.25 μm). Mass determination was carried out on a GC-Mass Agilent 5973 network equipped with a mass-selective detector.

Catalyst preparation

Synthesis of $[Mo_3S_4Cl_3(dmen)_3]BF_4$: A fivefold excess of PPh_3 (108 mg, 0.413 mmol) was added to an orange suspension of $(n\text{Bu}_4\text{N})_2[\text{Mo}_3\text{S}_7\text{Cl}_6]$ (100 mg, 0.083 mmol) in CH_3CN (12 mL) under nitrogen. The color of the solution turned green

immediately. After the reaction mixture had been stirring for 30 minutes, dmen (30 μL, 0.276 mmol) was added, which led to a color change from green to brown. Immediately, a freshly prepared 0.5 M solution of HBF_4·ether complex (0.66 mL, 0.3306 mmol) in CH_3CN was added and the solution turned green. The reaction mixture was stirred at room temperature for 30 min. After filtration, the green solution was concentrated under reduced pressure and the desired product was precipitated by adding diethyl ether (50 mL). Finally, the green solid was separated by filtration and washed with a cold mixture of hexane/toluene (1:1, 30 mL), boiling hexane (30 mL), cold isopropanol (10 mL) and diethyl ether to yield an air-stable product that was characterized as $[Mo_3S_4Cl_3(dmen)_3]BF_4$ (54 mg, 75 % yield). Elemental analysis: calcd (%) for $Mo_3Cl_3S_4N_6C_{12}H_{36}BF_4$: C 16.50, H 4.15, N 9.62; found: C 16.57, H 4.30, N 9.58. ^{1}H NMR: δ = 2.20 (br, 3H, NH), 2.78 (d, 9H, CH_3, $^2J_{H\text{-}H(N)}$ = 5.6 Hz), 3.04 (m, 6H, CH_2), 3.61 (m, 3H, CH_2), 3.85 (d, 3H, CH_2; 9H, CH_3, $^2J_{H\text{-}H(N)}$ = 5.9 Hz), 6.34 ppm (br, 3H, NH); ^{13}C {^{1}H} NMR: δ = 44.22 (s, CH_3), 50.48 (s, CH_3), 52.42 (s, CH_2), 57.77 ppm (s, CH_2); ESIMS (CH_3CN, 20 V): *m/z*: 786.9 [M^+].

X-ray data collection and structure refinement

Suitable crystals for X-ray studies of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ salt were grown by slow evaporation of a sample solution in dichloromethane:diethyl ether (1:1). X-ray diffraction experiments were carried out on a Agilent Supernova diffractometer equipped with an Atlas CCD detector by using $Cu_{K\alpha}$ radiation (λ = 1.54184 Å). No instrument or crystal instabilities were observed during data collection.[21] Absorption corrections based on the multiscan method were applied.[22] The structures were solved by direct methods in SHELXS-97 and refined by the full-matrix method on the basis of F^2 with the program SHELXL-97 by using the OLEX software package.[23] Graphics were performed with the Diamond visual crystal structure information system software.[24] Crystal data for $[Mo_3S_4Cl_3(dmen)_3](BF_4)$·0.5 CH_2Cl_2:

$C_{12.5}H_{37}BCl_4F_4Mo_3N_6S_4$, M =916.15, orthorhombic; space group *Pccn*; a = 21.9457(3), b = 17.55239(19), c = 16.2584(2) Å; α = 90°, β =90°, γ = 90°; V = 6262.71(13) Å^3; T = 200.00(14) K; Z = 8; $\mu(Cu_{K\alpha})$ = 15.694 mm^{-1}; reflections collected/unique = 26562/5581 (R_{int} = 0.0548); final refinement converged with R_1 = 0.0514 and R_2 = 0.1295 for all reflections; goodness of fit = 1.148; max./min. residual electron density = 1.497/-0.665 e·Å^{-3}.

The structure was refined in the orthorhombic *Pccn* space group. The non-hydrogen atoms of the cluster and the counteranion were refined anisotropically, whereas the positions of all hydrogen atoms in the diamine ligands were generated geometrically, assigned isotropic thermal parameters, and allowed to ride on their respective parent carbon atoms. A half molecule of dichloromethane was found in the last Fourier map, which was refined anisotropically. The carbon atom of this molecule lies on a special position, and the chlorine atoms were disordered over two positions with 60:40 occupancies. Their hydrogen atoms were included at their idealized positions.

CCDC 1054643 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Catalytic Activity Test

General procedure for the reduction of nitroarenes: Under a nitrogen atmosphere, nitrobenzene (10 μL, 0.097 mmol), anisole (20 μL; added as an internal standard), and Ph_2SiH_2 (3.5 equiv.) were added to a green solution of $[Mo_3S_4Cl_3(dmen)_3]BF_4$ (4.4 mg, 0.0050 mmol) in deoxygenated MeOH (2 mL). The reaction mixture was stirred at room temperature for 18 h. Ethyl acetate (5 mL) was then added, and a sample was taken from the resulting brown solution to be analyzed by GC. All catalytic reactions were performed at least twice to ensure reproducibility. To determine the isolated yields of the anilines, the general procedure was scaled up

by the factor of five, and no internal standard was added. After completion of the reaction and dilution of the mixture with ethyl acetate (15 mL), 3 M NaOH (aq, 5 mL) was added and the reaction mixture was vigorously stirred for 3 h at room temperature. The mixture was then extracted with ethyl acetate (two times), and the combined organic layers were dried over anhydrous $MgSO_4$. Finally, the organic phase was filtered, concentrated, and purified by silica gel column chromatography (*n*-hexane/ethyl acetate mixtures) to give the corresponding anilines.

General procedure for the reduction of azo compounds: The general procedure described for the reduction of nitroarenes (see above) was applied with minor modifications. Ph_2SiH_2 (4.5 equiv.) was used and the reaction was held at T = 80 ºC for 6 h.

Acknowledgements

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Keywords: azo compounds • cluster compounds • molybdenum • nitroarenes • reduction

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SUPPORTING INFORMATION

A Mild and Chemoselective Reduction of Nitro and Azo Compounds Catalyzed by a Well-defined Mo_3S_4 Cluster Bearing Diamine Ligands

Elena Pedrajas, Iván Sorribes, Kathrin Junge, Matthias Beller* and Rosa Llusar*

1. Catalyst characterization.

Figure SI1. ^{13}C NMR spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CD_2Cl_2.

Figure SI2. ^{1}H NMR spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CD_2Cl_2.

Figure SI3. ^{1}H-^{13}C gradient HSQC spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CD_2Cl_2.

Figure SI4. ESI mass spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CH_3CN at 20 V.

2. Conditions optimization for the reduction of nitrobenzene (1a) to aniline (2a).

Table SI1. Reductant testing for the Mo_3S_4-catalyzed transfer hydrogenation of **1a** to **2a**.

Table SI2. Influence of the solvent on the catalytic reduction of **1a** to **2a**.

Table SI3. Catalyst loading variation on the catalytic reduction of **1a** to **2a**.

Table SI4. Variation of the amount of Ph_2SiH_2 on the catalytic reduction of **1a** to **2a**.

3. ESI mass reaction monitoring of the reduction of nitrobenzene (1a) to aniline (2a) over time.

Figure SI5. ESI mass spectra from reaction monitoring of nitrobenzene (**1a**) reduction at a) t=0 min, b) t=30 min, and c) t=90 min.

4. Characterization data of the isolated products.

5. ^{1}H NMR and ^{13}C NMR spectra of the isolated products.

1. Characterization of the catalyst.

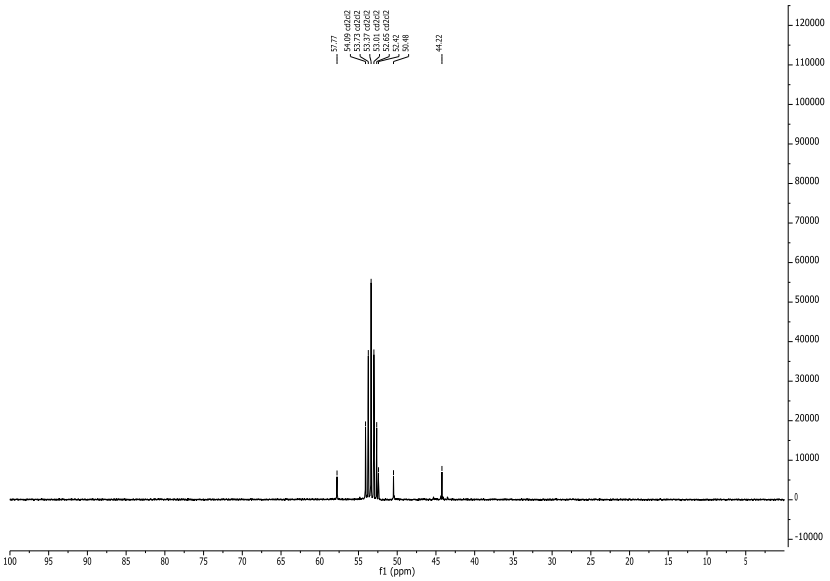


Figure SI1. ^{13}C NMR spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CD_2Cl_2

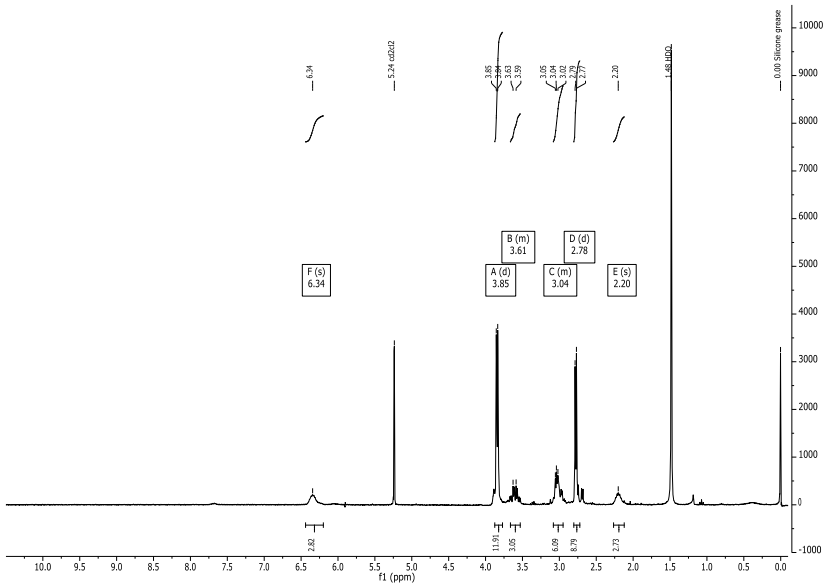


Figure SI2. ^{1}H NMR spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CD_2Cl_2.

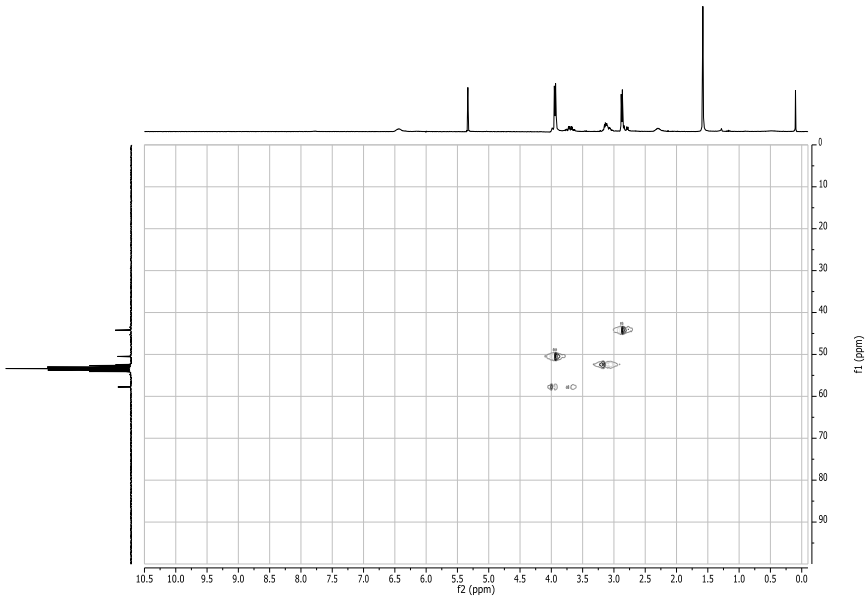


Figure SI3. ^{1}H-^{13}C gradient HSQC spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CD_2Cl_2.

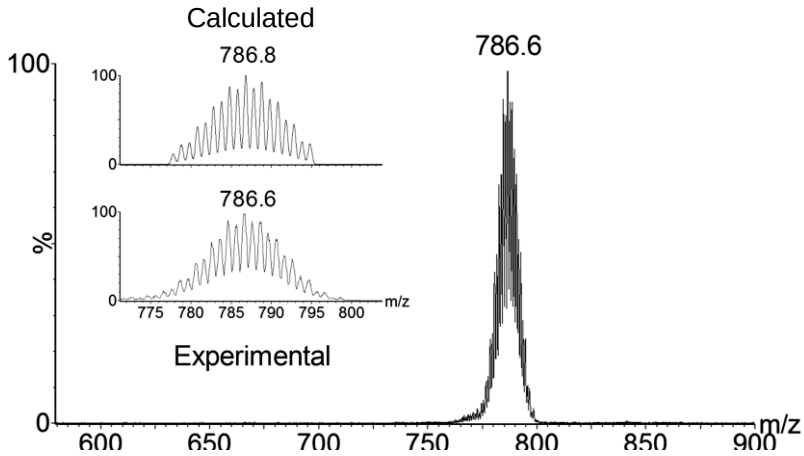
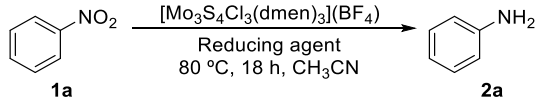


Figure SI4. ESI mass spectrum of the $[Mo_3S_4Cl_3(dmen)_3]BF_4$ complex in CH_3CN at 20 V.

2. Conditions optimization for the reduction of nitrobenzene (1a) to aniline (2a).

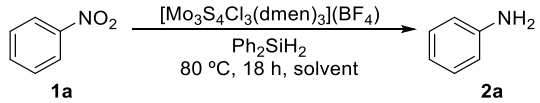
Table SI1. Reductant testing for the Mo_3S_4-catalyzed transfer hydrogenation of **1a** to **2a**.[a]



Entry	Reducing agent	Conversion [%][b]	Yield [%][b]
1	$HCOOH/Et_3N$ (5:2)	23	22
2[c]	$HCOO(NH_4)$	43	43
3	HCOOH	2	-
4[d]	Isopropanol/$CsCO_3$	-	-
5	-	-	-

[a] Reaction conditions: **1a** (0.1 mmol), reducing agent (3.5 equiv.), catalyst (5 mol%), CH_3CN (2 mL), 18 h, 80 ºC. [b] Determined by GC analysis using anisole as an internal standard. [c] Reducing agent (8 equiv.) [d] $CsCO_3$ (25 mol%).

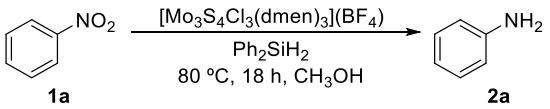
Table SI2. Influence of the solvent on the catalytic reduction of **1a** to **2a**.[a]



Entry	Solvent	Conversion [%][b]	Yield [%][b]
1	CH_3CN	>99	94
2	CH_3OH	>99	>99
3	EtOH	97	97
4	Isopropanol	83	82
5	THF	>99	94

[a] Reaction conditions: **1a** (0.1 mmol), Ph_2SiH_2 (3.5 equiv.), catalyst (5 mol%), solvent (2 mL), 18 h, 80 ºC. [b] Determined by GC analysis using anisole as an internal standard.

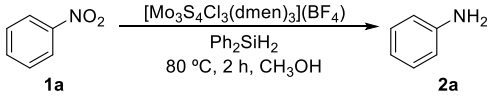
Table SI3. Catalyst loading variation on the catalytic reduction of **1a** to **2a**.[a]



Entry	Catalyst loading [mol%]	Conversion [%][b]	Yield [%][b]
1	-	-	-
2	1	55	55
3	2	61	61
4	3	92	89
5	4	95	92
6	5	>99	>99
7[c]	5	>99	>99

[a] Reaction conditions: **1a** (0.1 mmol), Ph_2SiH_2 (3.5 equiv.), CH_3OH (2 mL), 18 h, 80 ºC. [b] Determined by GC analysis using anisole as an internal standard. [c] Room temperature.

Table SI4. Variation of the amount of Ph_2SiH_2 on the catalytic reduction of **1a** to **2a**.[a]



Entry	Ph_2SiH_2 [equiv.]	Conversion [%][b]	Yield [%][b]
1	-	-	-
2	1	32	33
3	2	62	60
4	3	95	94
5	3.5	>99	>99

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (5 mol%), CH_3OH (2 mL), 2 h, 80 ºC. [b] Determined by GC analysis using anisole as an internal standard.

3. ESI mass reaction monitoring of the reduction of nitrobenzene (1a) to aniline (2a) over time.

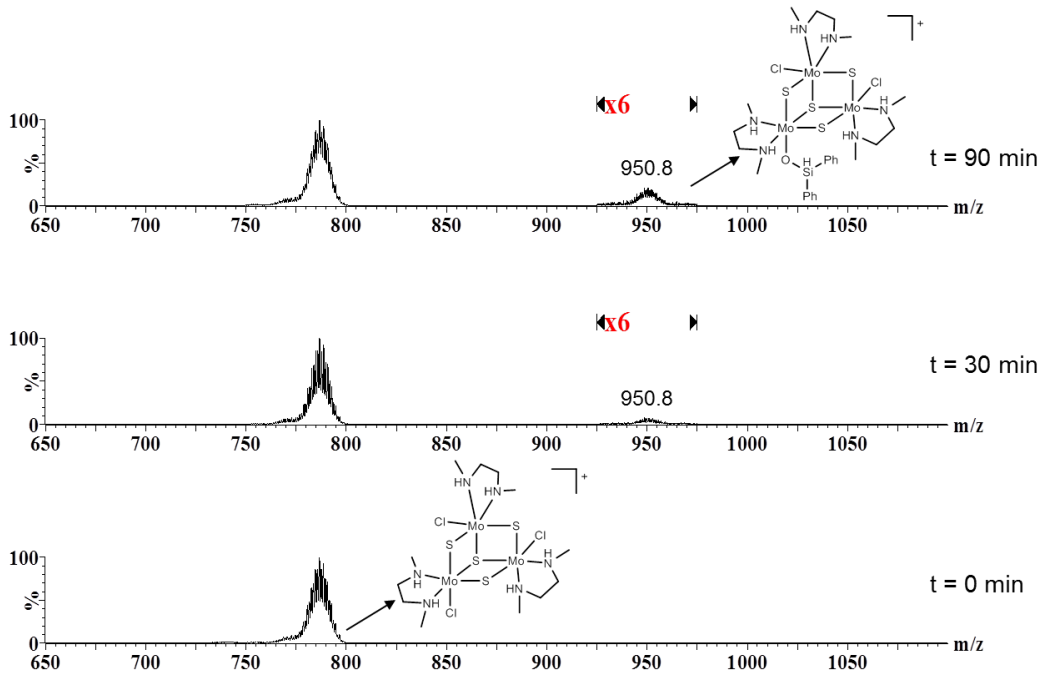
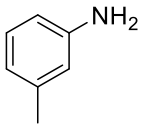


Figure SI5. ESI mass spectra from reaction monitoring of nitrobenzene (**1a**) reduction at a) t=0 min, b) t=30 min, and c) t=90 min.

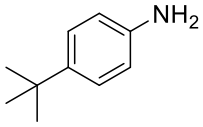
Figure SI5 shows the reaction monitoring of the reduction of **1a** under catalytic conditions at 80 ºC. In this in situ experiment the reaction mixture was re-examined over time for 90 min, whereupon almost a quantitative yield of **2a** was achieved. At room temperature (t = 0 min), a peak associated to the pseudomolecular $[Mo_3S_4Cl_3(dmen)_3]^+$ ion was observed, which remained largely unchanged over the time. After 30 min (up to 90 min), only an additional signal centered at m/z = 950.8 was also identified and assigned to the monosubstituted $[Mo_3S_4Cl_2(OSiHPh_2)(dmen)_3]^+$ ion complex on the basis of the m/z value as well as its characteristic isotopic pattern. Formation of this complex should come from reaction of $[Mo_3S_4Cl_3(dmen)_3]^+$ with siloxo species generated during reduction of the

nitro functionality. In fact, the relative intensity of this signal was increasing over time. Interestingly, no additional peaks associated to lower nuclearity molybdenum species were identified.

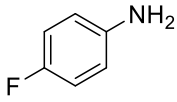
4. Characterization data of the isolated products.



3-methylaniline: isolated yield: 81%. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.02 (t, J = 7.7 Hz, 1H), 6.61 – 6.43 (m, 3H), 3.64 (br, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 146.71, 139.02, 128.97, 118.99, 115.54, 111.91, 21.07; MS (EI): m/z (rel. int.) 107.

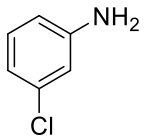


4-(tert-butyl)aniline: isolated yield: 90%.^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.28 – 7.17 (m, 2H), 6.72 – 6.60 (m, 2H), 3.55 (br, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.21, 141.05, 125.95, 114.63, 33.77, 31.33; MS (EI): m/z (rel. int.) 149.

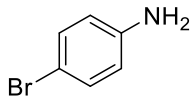


4-fluoroaniline: isolated yield: 85%. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.99 – 6.77 (m, 2H), 6.75 – 6.56 (m, 2H), 3.61 (br, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 157.70,

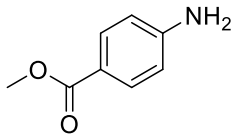
[154.60, 142.96 (d, $^1J_{C\text{-}F}$ = 878.5 Hz)], [115.78, 115.57 (d, $^3J_{C\text{-}F}$ = 16.33 Hz)], [115.68, 115.27 (d, $^2J_{C\text{-}F}$ = 31.21 Hz)]; MS (EI): *m/z* (rel. int.) 111.



3-chloroaniline: isolated yield: 85%. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.08 (t, *J* = 7.9 Hz, 1H), 6.78 – 6.64 (m, 2H), 6.57 (ddt, *J* = 8.0, 2.2, 0.8 Hz, 1H), 3.81 (br, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 148.11, 134.60, 130.29, 117.93, 114.54, 113.05; MS (EI): *m/z* (rel. int.) 127.

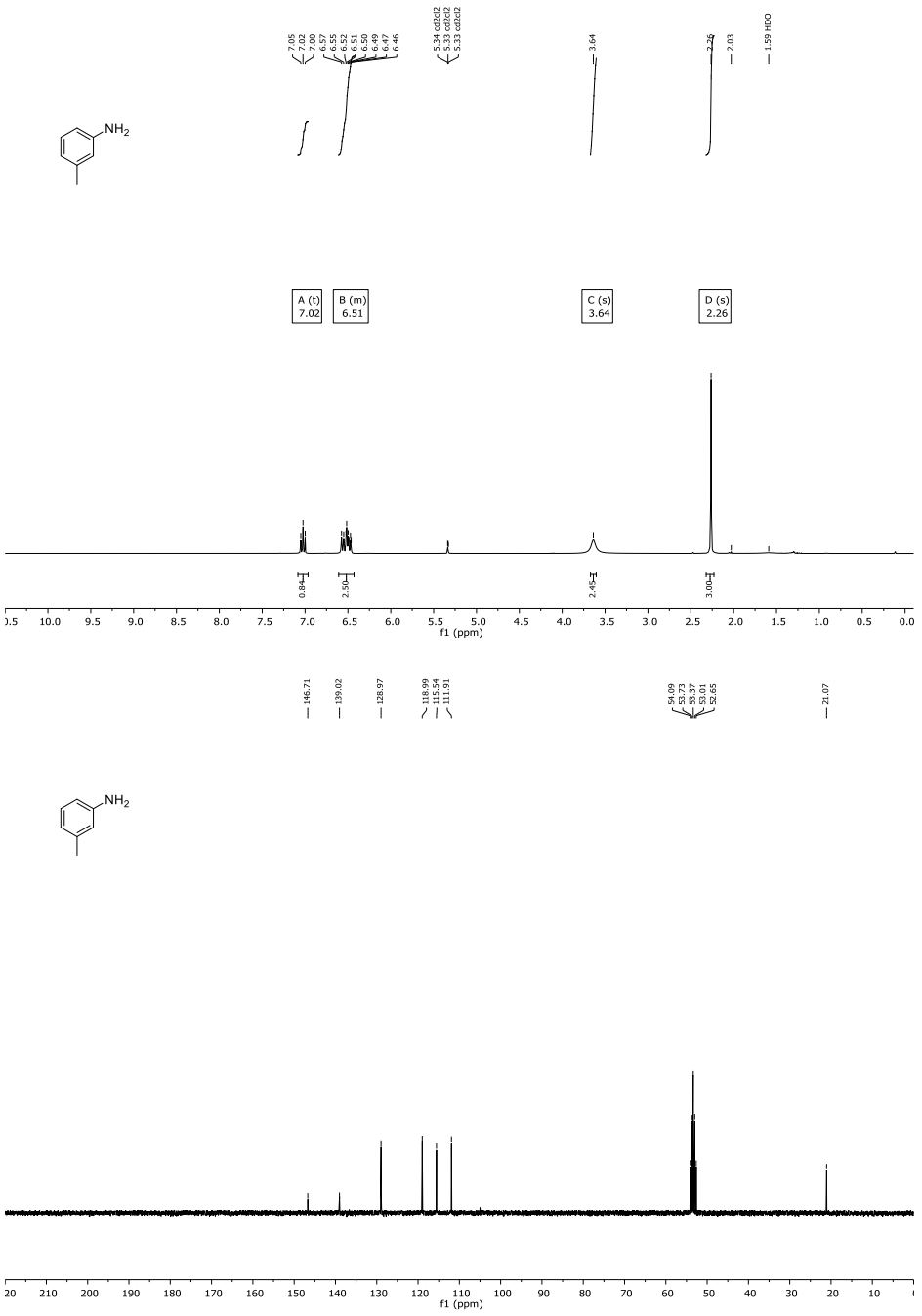


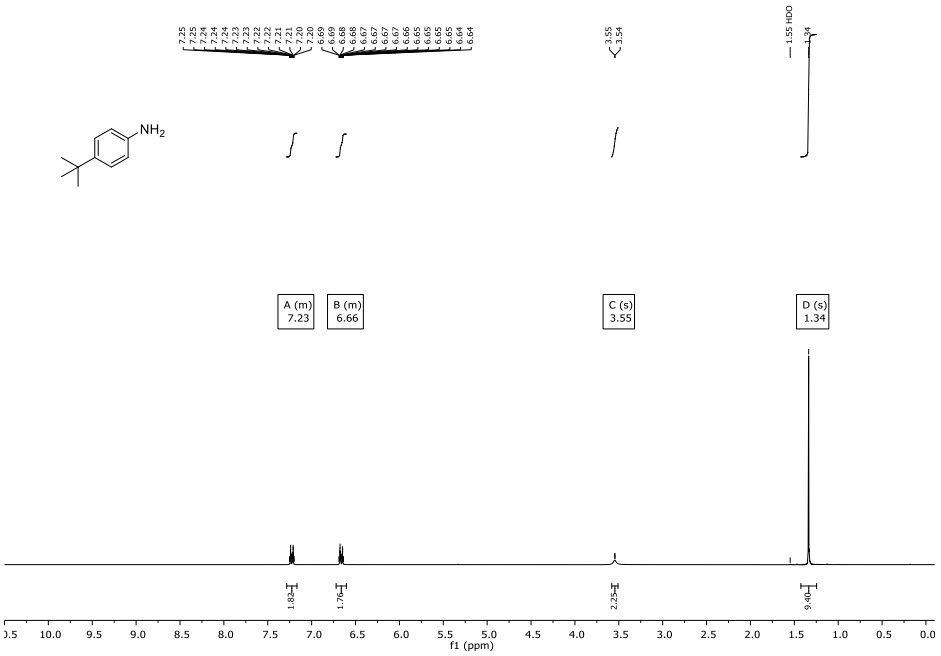
4-bromoaniline: isolated yield: 90%. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.30 – 7.18 (m, 2H), 6.66 – 6.52 (m, 2H), 3.71 (br, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 145.81, 131.86, 116.52, 109.66; MS (EI): *m/z* (rel. int.) 172.



methyl 4-aminobenzoate: isolated yield: 88%. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.88 – 7.75 (m, 2H), 6.72 – 6.60 (m, 2H), 4.16 (br, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 166.81, 151.14, 131.33, 119.51, 113.57, 51.31; MS (EI): *m/z* (rel. int.) 151.

5. ^{1}H NMR and ^{13}C NMR spectra of the isolated products.

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C (s) 3.55
D (s) 1.34
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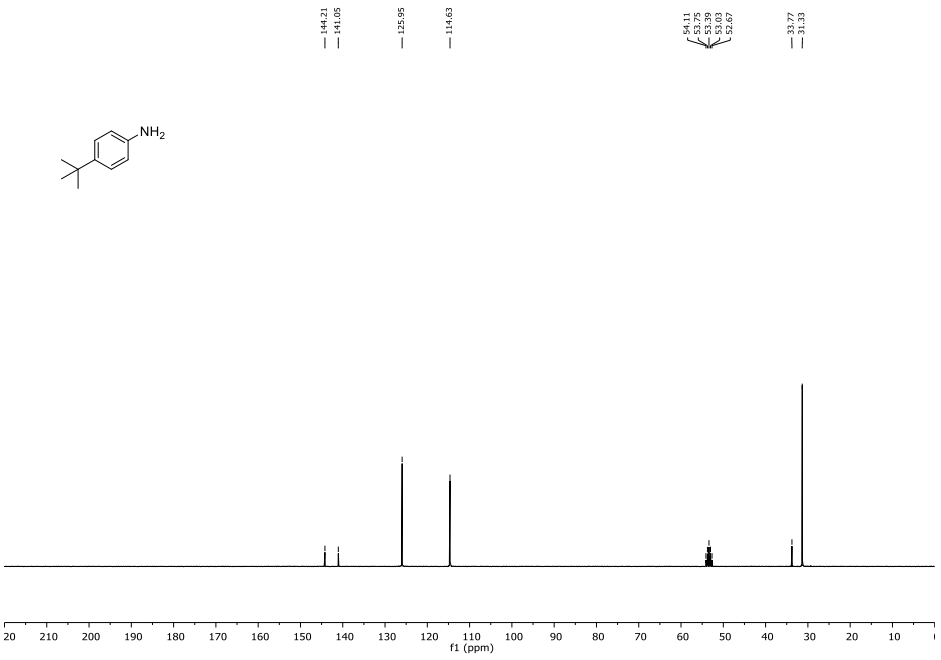
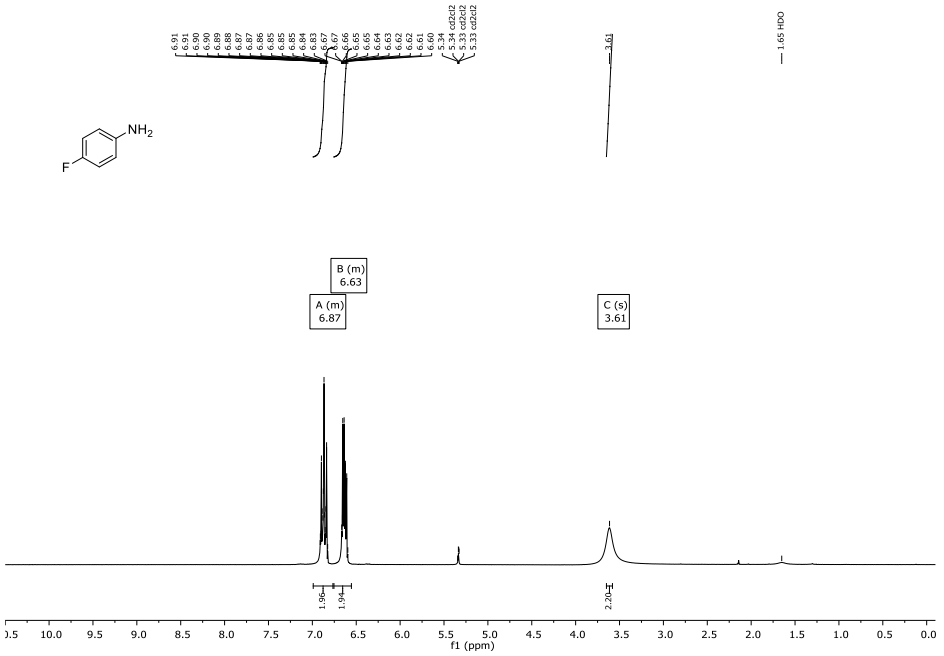
2.25
9.40
f1 (ppm)


NH2
f1 (ppm)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6.91
6.90
6.90
6.89
6.88
6.87
6.87
6.86
6.85
6.85
6.84
6.83
6.67
6.67
6.66
6.65
6.65
6.64
6.63
6.62
6.62
6.61
6.60
5.34 cd2cl2
5.34 cd2cl2
5.33 cd2cl2
5.33 cd2cl2
3.61
1.65 H2O
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F
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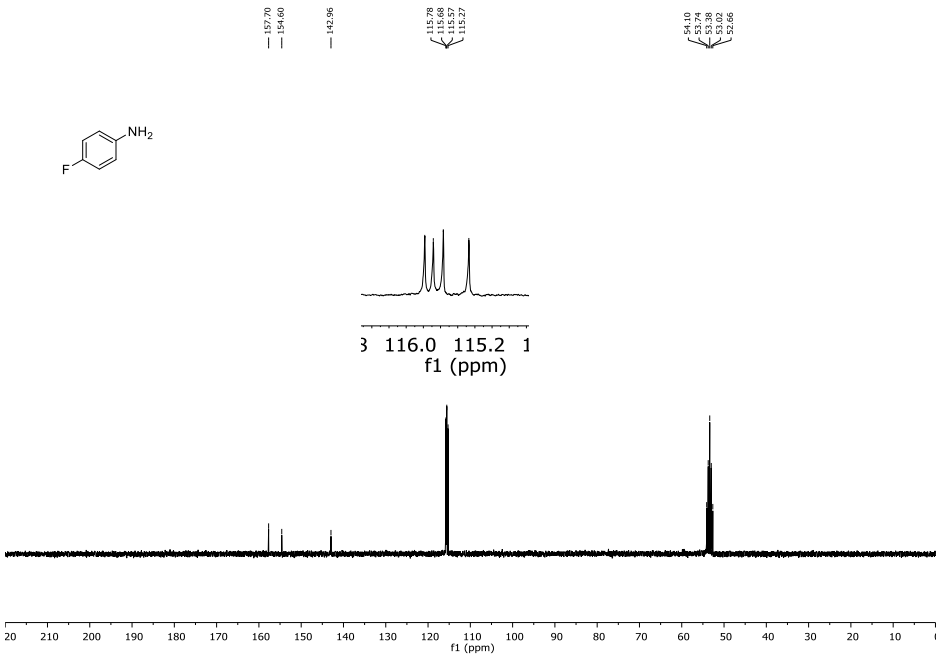
6.63
A (m)
6.87
C (s)
3.61
1.96
1.94
2.20
f1 (ppm)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142.96
115.78
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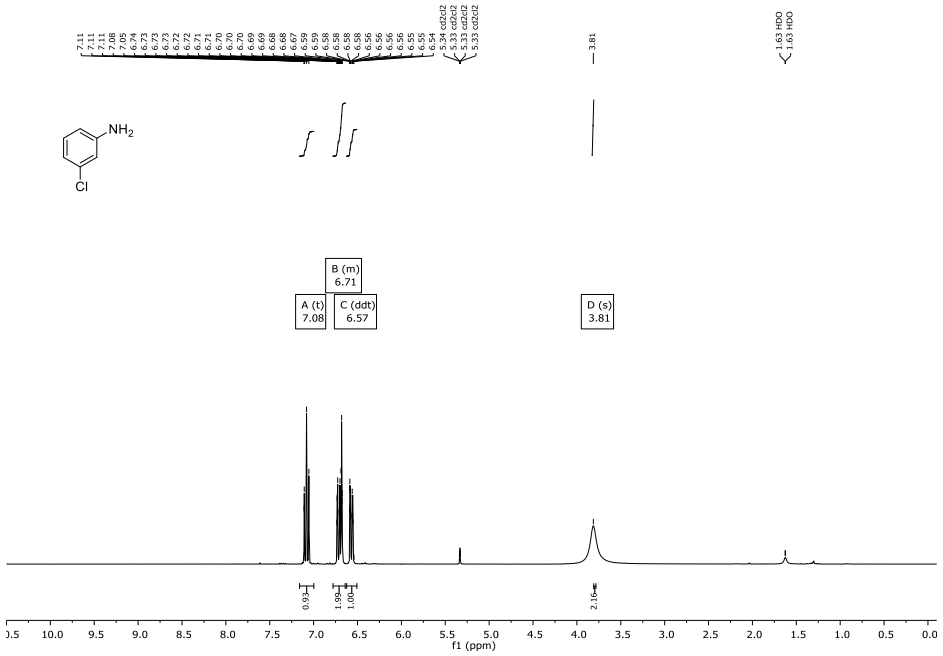
115.57
115.27
54.10
53.74
53.38
53.02
52.66
NH2
F
f1 (ppm)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Cl
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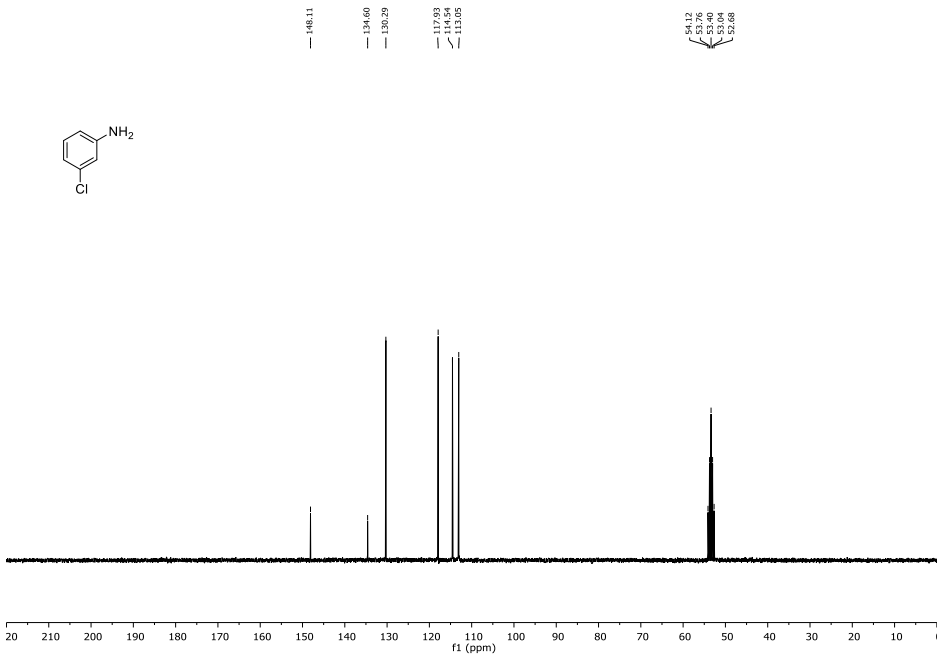
A (t) 7.08
C (ddt) 6.57
D (s) 3.81
f1 (ppm)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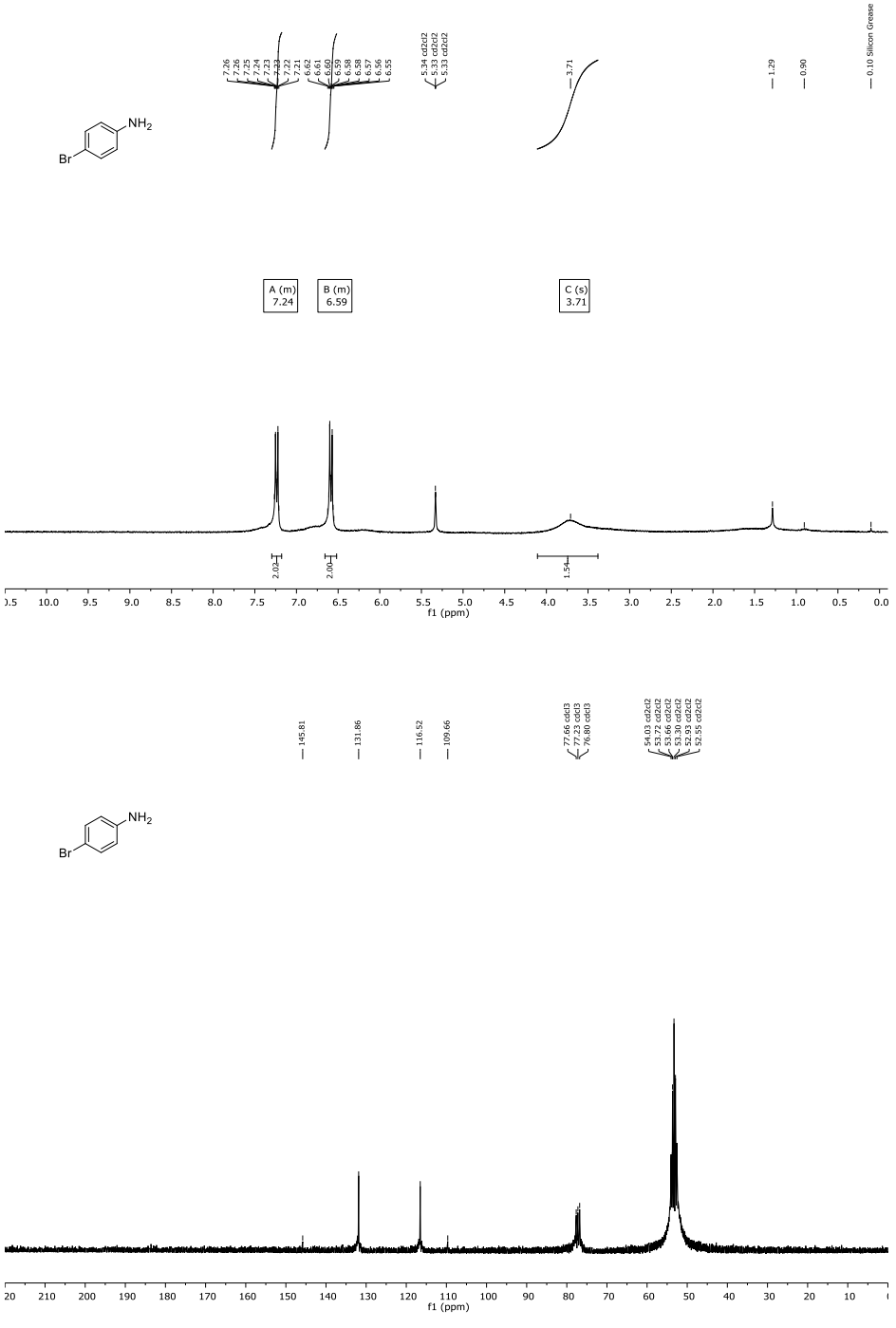
Cl
f1 (ppm)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Br
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7.26
7.25
7.24
7.23
7.23
7.22
7.21
6.62
6.61
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6.58
6.58
6.57
6.56
6.55
5.34 cd2d2
5.33 cd2d2
5.33 cd2d2
3.71
1.29
0.90
0.10 Silicon Grease
A (m)
7.24
B (m)
6.59
C (s)
3.71
2.02
2.00
1.54
f1 (ppm)
145.81
131.86
116.52
109.66
77.66 cdcl3
77.23 cdcl3
76.80 cdcl3
54.03 cd2d2
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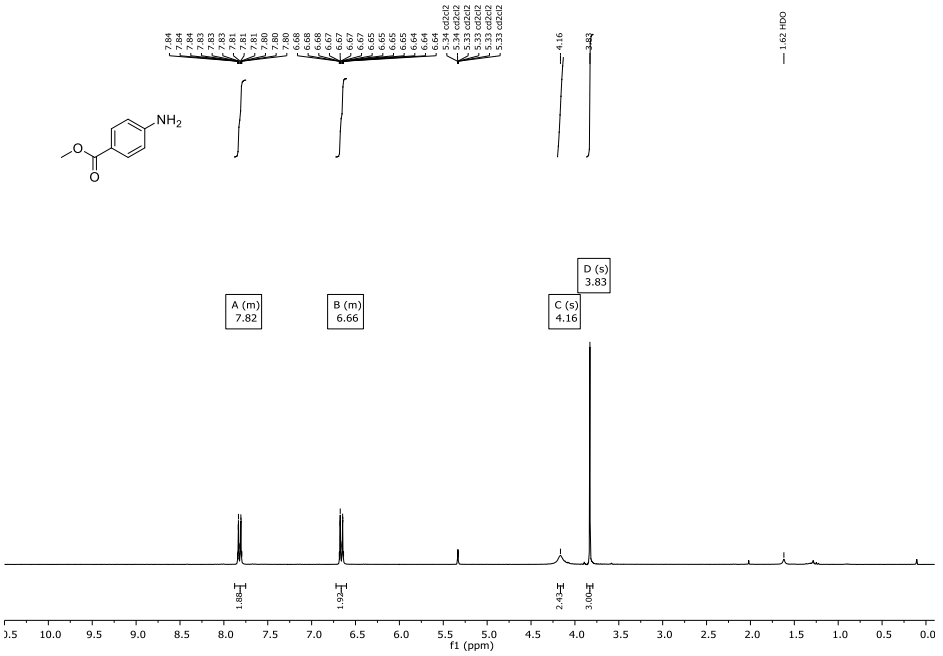
52.55 cd2d2
NH2
Br
f1 (ppm)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O
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C (s) 4.16
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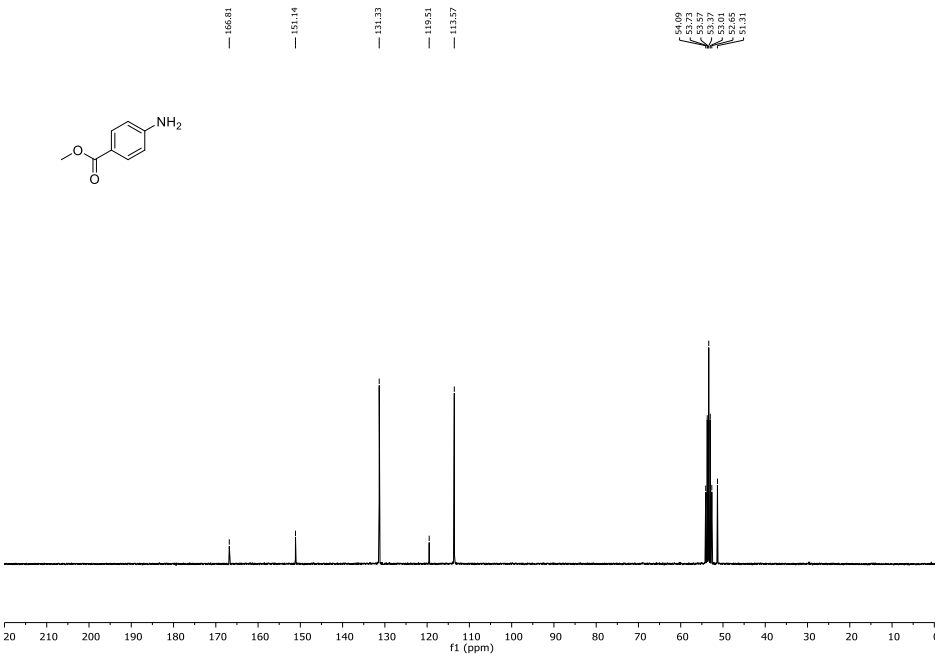
3.00
f1 (ppm)


166.81
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119.51
113.57
54.09
53.73
53.57
53.37
53.01
52.65
51.31
NH2
O
O
f1 (ppm)

4

Chemoselective hydrogenation of nitroarenes catalyzed by molybdenum sulphide clusters

4. Chemoselective hydrogenation of nitroarenes catalyzed by molybdenum sulphide clusters
    4.1. Manuscript
    4.2. Supporting Information

"Las dificultades aumentan cuanto más nos acercamos a la meta."

Johan Wolfgang von Goethe

Chemoselective Hydrogenation of Nitroarenes Catalylzed by Molybdenum Sulphide Clusters

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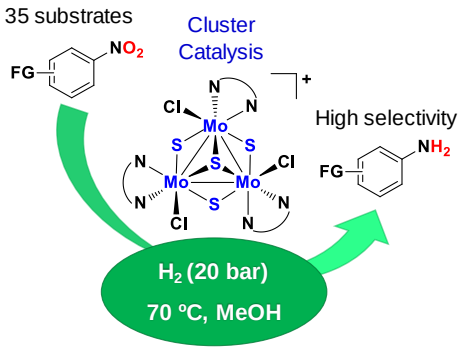


Growing the molybdenum cluster age: Well-defined diimino and diamino Mo_3S_4 cubane-type clusters are applied as chemoselective catalysts for the hydrogenation of functionalized nitroarenes. This atom efficient procedure allows for the preparation of anilines bearing synthetically relevant functional groups in high yields.

Abstract

Herein, we describe an atom efficient and general protocol for the chemoselective hydrogenation of nitroarenes to anilines catalyzed by well-defined diimino and diamino cubane-type Mo_3S_4 clusters. The novel diimino $[Mo_3S_4Cl_3(dnbpy)_3]^+$ ([**5**]$^+$) (dnbpy= 4,4'-dinonyl-2,2'-dipyridyl, L1) trinuclear complex was synthesized in high yields by simple ligand substitution reactions starting from the thiourea (tu) $[Mo_3S_4(tu)_8(H_2O)]Cl_4 \cdot 4H_2O$ (**3**) precursor. This strategy has also been successfully adapted for the isolation of the diamino $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ ([**6**](BF_4)), (dmen= N,N'-dimethylethylenediamine) salt. Applying these catalysts, high selectivity in the hydrogenation of functionalized nitroarenes has been accomplished. Over thirty anilines bearing synthetically functional groups have been synthesized in 70 to 99% yield. Notably, the integrity of the cluster core is preserved during catalysis. Based on kinetic studies on the hydrogenation of nitrobenzene and other potential reaction intermediates, the direct reduction to aniline is the preferential route.

Introduction

Catalytic hydrogenation is a fundamental methodology in catalysis widely used for the conversion of several raw materials to produce highly valuable chemicals.[1] In general, the success of this transformation relies on the use of transition metals as catalysts. In terms of industrial applications, heterogeneous catalysts are preferred because of their stability, ease of separation and recycling.[2] However, when the hydrogenation reaction has to be performed in a selective manner, the use of molecularly defined homogeneous catalysts is still an attractive approach. Notably, by choosing the right combination metal center and enclosing ligands their activity can be tuned to control the selectivity towards the desired product.

One of the most fundamental hydrogenation reactions in chemistry involves the use of nitroarenes as starting materials, since the resulting anilines are key building

blocks and central intermediates for the chemical, pharmaceutical and agrochemical industries.[3–5] Despite of the significant progress achieved during last decades in both homogeneous[6–14]and heterogeneous catalysis,[15–27] the environmentally benign chemoselective hydrogenation of nitroarenes conducted at mild conditions and using non-noble metal based catalysts remains an actual and important topic for both academia and industry.

Typically in academia, homogeneous catalytic hydrogenations of nitroarenes and related compounds make use of noble metals,[28] although economic and environmental reasons are more recently boosting the development of earth-abundant metal-based catalysts such as iron, cobalt and to a lesser extent, molybdenum.[29–40] In fact, examples of molybdenum-catalyzed homogeneous hydrogenations are scarce. In the mid-eighties, the group of Dubois reported the hydrogenation of a few nitroarenes, nitrosobenzene, phenylhydroxylamine, and azoxybenzene by using dinuclear molybdenum(IV) complexes containing bridging sulphide ligands as catalysts.[41] These $MeCpMo(\mu\text{-}S)_2(\mu\text{-}SH)_2MoCpMe$ complexes or closely related dimers, are also active for the hydrogenation of N=N bonds in azides and azo compounds as well as for the reduction of C=N bonds in isocyanates, isothiocyanates, and imines. Although such clusters were able to hydrogenate different unsaturated nitrogen functional groups, their selectivity was not evaluated when other reactive groups were present.

Later on, Bullok and co-workers showed that mononuclear hydrido molybdenum carbonyl complexes were active catalysts for the ionic hydrogenation of ketones under mild conditions.[42] In this respect, the work of Martins on related molybdenum complexes is also noteworthy.[43] In addition, Royo and co-workers applied simple MoO_2Cl_2 for the catalytic hydrogenation of alkynes, sulfoxides, and nitroarenes. Harsh conditions were required, however, for the nitroarene hydrogenation (120 ºC; 50 atm of H_2).[44,45] In 2009, Baricelli *et al.* presented the

hydrogenation of olefins catalyzed by a molybdenum carbonyl mononuclear complex.[46] More recently, this transformation and the hydrogenation of imines were also accomplished by using molybdenum nitrosyl hydrides as catalysts.[47,48]

Generally, catalytic systems based on transition metal clusters have been developed along the past decades to a much lesser extent than their monometallic counterparts.[49] However, in 2012 we described cubane-type $Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3$ clusters functionalized with diphosphane ligands for the selective transfer hydrogenation of nitroarenes applying formates as reducing agents.[50] The same cluster unit decorated with diamine ligands has been used for the selective catalytic hydrosilylation of nitro and azo compounds under mild conditions.[51] Although both systems are attractive for the synthesis of specific anilines at laboratory scale, they suffer from low atom-efficiency. Therefore, we became interested in developing a more environmentally benign catalytic system that makes use of molecular hydrogen, which is a cheap and "green" reducing agent. Motivated by the early work of Dubois on $Mo_2(\mu\text{-}S)_2(\mu\text{-}SH)_2$ and the electronic and structural similarities between these dimers and the cubane-type $Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3$ clusters, we decided to investigate the catalytic potential of these trimetallic complexes in the presence of various bidentate ligands. In this context, herein, we report for the first time the direct hydrogenation of aromatic nitro compounds catalyzed by well-defined Mo_3S_4 clusters bearing diimine and diamine ligands.

Results and Discussion

Synthesis and characterization of the catalyst

In an exploratory study aimed to identify active species in the hydrogenation of nitrobenzene (**1a**), we tested several trinuclear molybdenum sulphide clusters, represented in Fig. 1, as catalysts. The Mo_3S_4 and Mo_3S_7 cluster cores differ in the nature of the bridging ligand, sulphide or disulphide. The nine outer positions in

Mo_3S_4 and the six ones in Mo_3S_7 are occupied by groups of different nature: chloride, disulphide, thiourea and water. For comparative purposes, the one dimensional $\{Mo_3S_7Cl_4\}_n$ polymeric phase has also been tested.

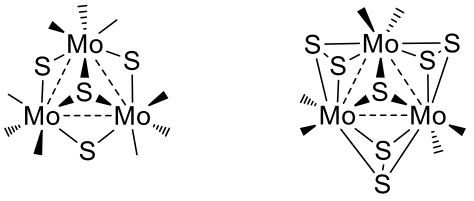
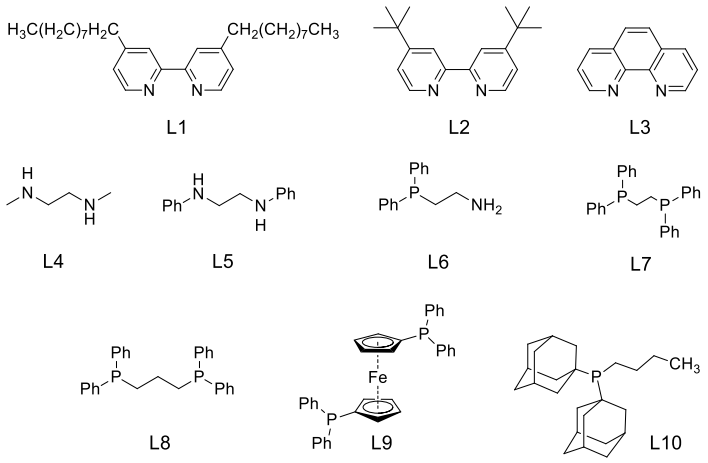


Figure 1. Mo_3S_4 and Mo_3S_7 cluster units.

As shown in Table 1 (entries 1-4), the trinuclear complex $[Mo_3S_4(tu)_8(H_2O)]Cl_4 \cdot 4H_2O$ (**3**) (tu = thiourea) dissolved in methanol proved to be the most active system in the hydrogenation of this model substrate (**1a**) at 20 bar of H_2 and 80 ºC affording aniline (**2a**) in 44% yield (Table 1, entry 3). To improve the product yield, various commercially available phosphine and nitrogen-based ligands, shown in Scheme 1, were tested in combination with the thiourea Mo_3S_4 complex **3** (Table 1, entries 5-14).

In this particular case, the use of phosphorous-based ligands led to a detrimental activity. However, in the presence of the diimine, 4,4'-dinonyl-2,2'-dipyridyl (dnbpy; **L1**), 4,4'-di-tert-butyl-2,2'-dipyridyl (dbbpy; **L2**) or diamine *N,N'*-dimethylethylenediamine (dmen; **L4**) ligands, the yield was improved up to 98-99% (Table 1, entries 5, 6, 8). Advantageously, compared to the existing homogeneous Fe-based catalyst system reported to date for the hydrogenation of nitroarenes, no stoichiometric amounts of strong acids such as trifluoroacetic acid are required to achieve significant reactivity.[6] As expected, no reactivity was observed for the ligand-catalyzed reaction in the absence of complex **3** (Table 1, entry 15). Hence, we focused our attention on the catalytic activity of the well-defined $[Mo_3S_4Cl_3L_3]^+$ cluster, L = dnbpy (**L1**), and its analogous dmen (**L4**)] derivative.[51]



Scheme 1. Ligands tested in combination with complex **3** on the catalytic hydrogenation of nitrobenzene (**1a**) to aniline (**2a**).

For the synthesis of the new diimino $[Mo_3S_4Cl_3(dnbpy)_3]^+$ (**[5]**$^+$) cluster, we followed the general procedure developed by some of us for the preparation of diimino Mo_3S_4 complexes functionalized with 2,2'-bipyridine and 1,10-phenanthroline (**L3**) ligands, according to equation 1.[52]

$[Mo_3S_4(tu)_8(H_2O)]Cl_4 \cdot 4H_2O$ (**3**) + 3 dnbpy (excess) →

→ $[Mo_3S_4Cl_3(dnbpy)_3]^+$ (**[5]**$^+$) + 8 tu + H_2O **(1)**

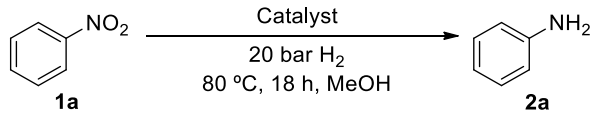
This reaction took place in acetonitrile under reflux conditions. After removal of the solvent, the product was extracted with CH_2Cl_2 to eliminate the free thiourea ligand, and further purified by silica-gel chromatography column to afford the **[5]**(PF_6) salt in 80% yield. Its positive ESI mass spectrum in CH_3CN shows one single charged peak at m/z = 1748, which is associated to the pseudomolecular $[Mo_3S_4Cl_3(dnbpy)_3]^+$ (**[5]**$^+$) ion on the basis of the m/z value and its characteristic isotopic pattern. Unfortunately, the presence of long alkyl chains in the **[5]**$^+$ cation precluded crystallization of any of its salts. The molecular structure of **[5]**$^+$ is similar

to that of other diimine and diamine derivatives of the cuboidal Mo_3S_4 cluster core according to NMR spectroscopy. The asymmetric coordination of the ligands to the $Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3$ core with one nitrogen atom attached *trans* and the other one *cis* to the capping sulfur atom (μ_3-S) is confirmed by six different signals of the dnbpy ligand (**L1**) in the aromatic region of the ^{1}H NMR spectrum (Figure SI1). The ^{13}C NMR spectrum, with ten different signals corresponding to the non-equivalent aromatic rings of **L1**, also confirms this structural arrangement (Figure SI2).

Incidentally, this synthetic strategy can be used for the isolation of the $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (**[6]**(BF_4)) salt, previously prepared from *in situ* generated $[Mo_3S_4Cl_x(PPh_3)_y(solvent)_z]^{(4-x)+}$ species.[51] In the case of the diamino **[6]**$^+$ cation, acid must be added to prevent partial substitution of the terminal chlorine ligands by hydroxo groups generated from adventitious water molecules.

With well-defined complexes **[5]**(PF_6) and **[6]**(BF_4) in hand, we tested them as catalysts for the hydrogenation of nitrobenzene (**1a**) under the same reaction conditions used *vide supra* (Table 1, entries 16, 17). Both complexes showed similar reactivity compared with their corresponding *in situ* systems, thus revealing that identical active species are formed.

Table 1. Molybdenum sulphide-catalyzed hydrogenation of nitrobenzene.[a]



Entry	Catalyst	Conv. [%][b]	Yield [%][b]
1	$(TBA)_2[Mo_3S_7Cl_6]$ (**1**)	12	12
2	$(NH_4)_2(Mo_3S_{13})2H_2O$ (**2**)	0	0
3	$[Mo_3S_4(tu)_8(H_2O)]Cl_4 \cdot 4H_2O$ (**3**)	46	44
4	$\{Mo_3S_7Cl_4\}_n$ (**4**)	1	1
5[c]	**3**/L1	>99	>99
6[c]	**3**/L2	>99	>99
7[c]	**3**/L3	16	15
8[c]	**3**/L4	>99	98
9[c]	**3**/L5	22	22
10[c, d]	**3**/L6	29	29
11[c, d]	**3**/L7	18	11
12[c, d]	**3**/L8	32	13
13[c, d]	**3**/L9	34	26
14[c, d]	**3**/L10	19	12
15	L1	-	-

Entry	Catalyst	Conv. [%][b]	Yield [%][b]
16	**[5]**(PF_6)	>99	98
17	**[6]**(BF_4)	>99	>99
18[c]	**[5]**(PF_6)	>99	>99
19[f]	**[5]**(PF_6)	52	52

[a] Reaction conditions: Nitrobenzene (0.1 mmol), H_2 (20 bar), catalyst (5 mol%), MeOH (2 mL), 18 h, 80 ºC. [b] Determined by GC analysis using *n*-hexadecane as an internal standard. [c] **3**/Ligand (1:3.5). [d] 100 ºC. [e] Catalyst (4 mol%), 70 ºC. [f] Catalyst was reused for the second time.

Therefore, experiments for further optimization of reaction conditions were conducted using these well-defined complexes as catalysts. Comparing **[5]**$^+$ and **[6]**$^+$, the diimino complex showed a slightly higher reactivity at lower reaction temperatures (Table SI1), and a quantitative yield of aniline (**2a**) was achieved at 70 ºC (Table 1, entries 17-18) for both catalysts. Next, the influence of the H_2 pressure, solvent and catalyst loading was studied in the presence of catalyst **[5]**(PF_6). Interestingly, only a slight decrease of conversion and yield (89% of **2a**) was observed by decreasing the H_2 pressure up to 15 bar (Table SI2). The use of other solvents different from methanol led to a detrimental conversion of **1a**. Whereas good reactivity was achieved with ethanol, other polar solvents, such as CH_3CN and isopropanol, afforded significantly lower yields of **2a**. No reaction took place in non-polar solvents as a consequence of the low solubility of catalyst **[5]**(PF_6) (Table SI3). Notably, no deuterated aniline was formed by using CD_3OD as solvent, thus precluding a solvent-mediated transfer hydrogenation mechanism (see, Figure SI4 in the Supporting Information). Finally, an optimal catalyst loading was found to be 4 mol%, affording **2a** in quantitative yield at 20 bar of H_2, 70 ºC and using methanol as solvent (Table 1, entry18; see also Table SI4).

Next, a reaction profile of the hydrogenation of **1a** was performed under standard reaction conditions using different batch experiments (Figure 2). To our delight, no accumulation of the carcinogenic and potentially explosive hydroxylamine (< 1%) was observed during catalysis. Notably, no obvious induction period is observed from the reaction profile, thus suggesting that no fragmentation of the trinuclear cluster entity to lower nuclearity molybdenum complexes is required to form the active species in the reaction mixture.

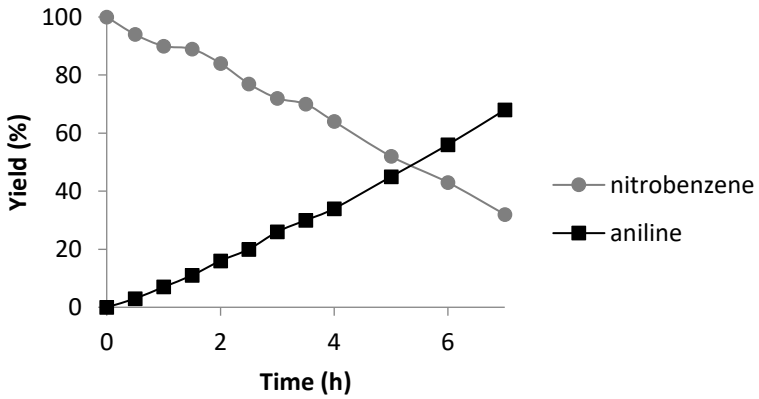


Figure 2. Concentration/time diagram for the hydrogenation of nitrobenzene (**1a**) to aniline (**2a**) catalyzed by the diimino $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ (**[5](PF$_6$)**) complex.

To obtain further evidence about the cluster integrity during catalysis, reaction mixtures obtained from batch experiments at different reaction times were analyzed by electrospray ionization mass spectrometry (ESI-MS) after dilution with ethyl acetate. As shown in Figure 3 (see also Figure SI5), the peak centered at m/z = 1748 associated to the pseudomolecular $[Mo_3S_4Cl_3(dnbpy)_3]^+$ (**[5]$^+$**) ion is successively broadened with the reaction time as a consequence of the formation of trinuclear species of general formula $[Mo_3S_4Cl_{3-x}(OMe)_x(dnbpy)_3]^+$. Apparently, all these mixed outer-ligands clusters remain active during the catalytic reaction. No other peaks were observed even after longer reaction time (4 h). Therefore, we decided to perform the catalyst recycling in the model reaction after recovering the

catalyst by evaporation of the reaction mixture. Interestingly, a moderate yield of **2a** (52%) could be still obtained in a second run (Table 1, entry 19).

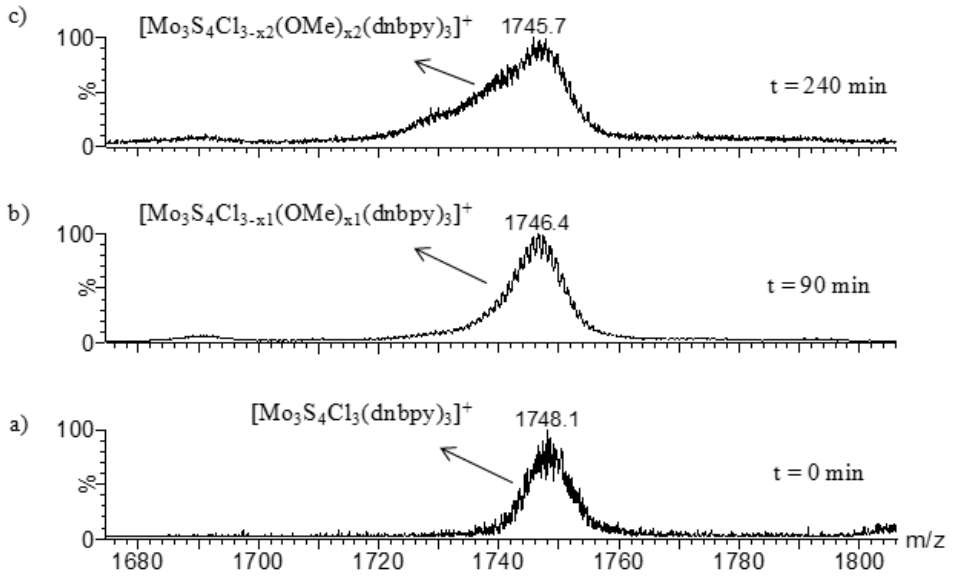


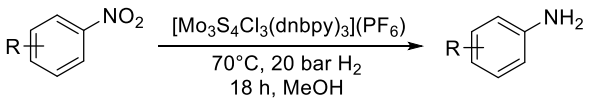
Figure 3. ESI mass spectra from nitrobenzene hydrogenation monitoring (a: t = 0 min; b: t = 90 min and c: t = 240 min ($x_2 > x_1$)).

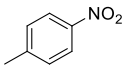
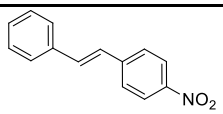
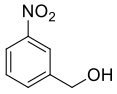
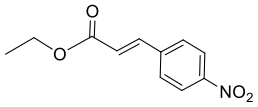
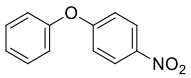
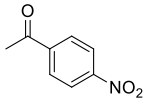
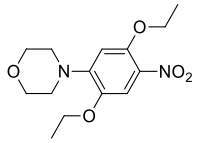
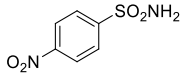
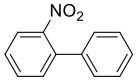
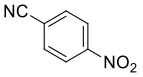
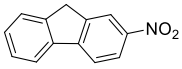
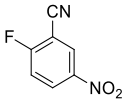
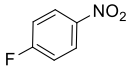
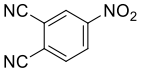
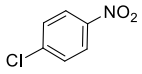
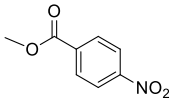
Since no intermediates could be detected by quenching the reaction at shorter times (see Figure 2), the hydrogenation of some potential intermediates, such as *N*-phenylhydroxylamine, nitrosobenzene, azoxybenzene, and azobenzene were conducted in the presence of **[5]**(PF_6). In all cases, full conversions of the starting material and nearly quantitative yield of aniline (**2a**) were obtained. Thus, both generally accepted reaction pathways, the direct reduction to aniline or the dimerization via azobenzene,[53] seem to be possible in the present reaction system (Table SI5 and Scheme SI1). To differentiate between both routes, kinetic studies starting from nitrobenzene, azoxybenzene and azobenzene have been undertaken (Figure SI6). Reaction monitoring for the nitrobenzene and azobenzene hydrogenation shows aniline as the only reaction product while both aniline and

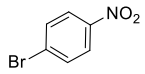
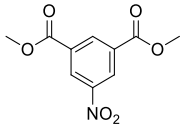
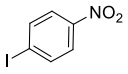
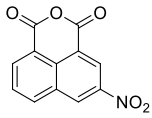
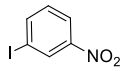
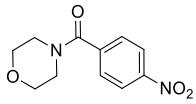
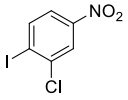
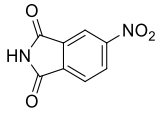
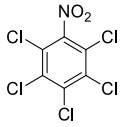
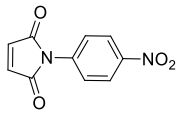
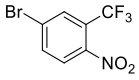
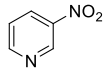
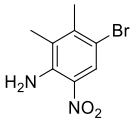
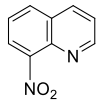
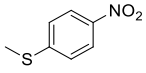
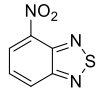
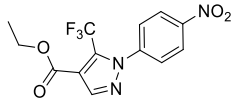
azobenzene are detected in the azoxybenzene hydrogenation. Reaction rates for the nitrobenzene hydrogenation range between 3,5-4,9 mmol L^{-1} h^{-1} which are two to three times higher than the rates for the azoxybenzene and azobenzene hydrogenation. That is, the direct reduction to aniline is the preferential route. Incidentally, the same reaction pathway is found to be kinetically favored for the heterogeneous nitrobenzene reduction with hydrazine catalyzed by oxygen-implanted molybdenum disulphide.[54]

Next, the applicability of the well-defined catalyst $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ (**[5]**(PF_6)) was demonstrated in the hydrogenation of more than 30 structurally diverse nitroarenes. As shown in Table 2, nitroarenes bearing inert and/or less reactive functional groups, such as alkyl, hydroxy, alkoxy and biphenyl, were hydrogenated giving the corresponding anilines in up to quantitative yields (Table 2, entries 1-6). Industrially relevant halogen-substituted nitroarenes were smoothly hydrogenated without any dehalogenation process affording the desired halogen-substituted anilines in excellent yields, independently of the number of halogens and their ring position (Table 2, entries 7-13). In addition, other substituents including trifluoromethyl and amino as well as thiomethyl groups were well tolerated, too (Table 2, entries 14-16).

Table 2. Mo_3S_4-catalyzed hydrogenation of different nitroarenes.[a]



Entry	Substrate	Conv. (%)[b]	Yield (%)[b]	Entry	Substrate	Conv. (%)[b]	Yield (%)[b]
1		>99	>99	18		>99	95
2		>99	>99	19		>99	87
3		>99	90 (80)	20		>99	94
4		>99	>99	21		>99	80
5[c]		>99	97 (90)	22		>99	>99 (96)
6[c]		99	98 (91)	23		>99	94 (87)
7[c]		>99	95	24		>99	88
8		>99	92 (80)	25		>99	80

9		>99	99 (89)	26		>99	94
10[d]		>99	96 (80)	27		>99	(99)
11		>99	98	28		>99	88
12		>99	93	29		>99	(95)
13		>99	>99	30		>99	70
14		>99	>99	31[c]		>99	91
15		>99	>99	32		>99	>99
16		>99	84	33		>99	97 (93)
17		98	85	34		>99	>99

[a]Reaction conditions: nitroarene (0.1 mmol), 20 bar H_2, catalyst (5 mol%), MeOH (2 mL), 18 h, 70 ºC. [b]Determined by GC analysis using *n*-hexadecane as an internal standard; yields of isolated products given in parentheses. [c]100 ºC. [d]35 bar H_2.

More demanding is hydrogenation of nitroarenes containing easily reducible functional groups. For instance, the chemoselective reduction in the presence of olefins continues to be challenging.[17] Remarkably, olefinic double bonds were retained affording the corresponding anilines in high yields (Table 2, entries 17-19). Interestingly, other nitroarenes containing sensitive groups, such as ketones or sulfonamides, were converted into the corresponding anilines in good to excellent yields (Table 2, entries 20, 21). Moreover, carboxylic acids derivatives, such as cyanides, esters and amides were also tolerated (Table 2, entries 22-30). Finally, several heteroaromatic amines, which are valuable building blocks for the preparation of a variety of agrochemicals and pharmaceuticals,[55] were afforded in 91-99% yield without further optimization (Table 2, entries 31-34).

Conclusions

In conclusion, well-defined diimino and diamino Mo_3S_4 cubane-type clusters have been established as excellent catalysts for the hydrogenation of functionalized nitroarenes. Notably, the procedure is highly chemoselective in the presence of other reducible functional groups. A variety of anilines containing synthetically relevant functional groups are obtained in good to excellent yields. Reaction monitoring and electrospray ionization mass spectrometric measurements support the integrity of the cluster unit during catalysis.

Experimental Section

Catalyst Preparation

Synthesis of $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$: A mixture of $[Mo_3S_4(tu)_8(H_2O)]Cl_4{\cdot}4H_2O$ (0.40 g, 0.32 mmol), 4,4'-dinonyl-2,2'-bipyridine (0.42 g, 1.0 mmol), and CH_3CN (40 mL) was refluxed for 4-5 hours. After cooling to room temperature, the reaction mixture was taken to dryness, redissolved in CH_2Cl_2 and the non-soluble thiourea was eliminated by filtration. The solution of $[Mo_3S_4Cl_3(dnbpy)_3]Cl$ was loaded onto a

silica gel column. After the column was washed with CH_2Cl_2, elution with a solution of KPF_6 in acetone (10 mg mL^{-1}) afforded a concentrated brown solution, which was evaporated to dryness, redissolved in CH_2Cl_2 and filtered in order to eliminate the inorganic salts. Finally, the resulting solution was allowed to evaporate slowly in air to give 0.48 g (80%) of the desired complex as a brown solid. $C_{84}H_{132}N_6Cl_3F_6Mo_3PS_4$ (1896.53): Elemental analysis (%) calcd.: C 53.3, H 7.0, N 4.4; found: C 54.4, H 7.6, N 4.7; ^{1}H NMR (500 MHz, 298 K, CD_2Cl_2): δ = 10.40 (d, J = 5.9 Hz, 3H); 9.60 (d, J = 5.9 Hz, 3H); 8.43 (s, 3H); 8.17 (s, 3H); 7.64 (d, J = 5.8 Hz, 3H); 7.30 (d, J = 5.8 Hz, 3H); 3.03 (t, J = 7.8 Hz, 6H); 2.82 (t, J = 7.8 Hz, 6H); 1.90 (p, J_{12} = 7.8, J_{23} = 7.6 Hz, 6H); 1.75 (p, J_{12} = 7.5, J_{23} = 7.7 Hz, 6H); 1.53 (p, J_{12} = 7.5, J_{23} = 7.3 Hz, 6H); 1.45 (p, J_{12} = 7.6, J_{23} = 7.2 Hz, 6H); 1.33 (m, 60H); 0.93 (m, 18H) ppm. ^{13}C{^{1}H} NMR (500 MHz, 298 K, CD_2Cl_2): δ= 14.43 (s, CH_3), 23.23 (s, CH_2), 29.85 (s, CH_2), 30.54 (s, CH_2), 30.75 (s, CH_2), 32.44 (s, CH_2), 36.19 (s, CH_2), 123.09 (s, CH), 124.98 (s, CH), 126.87 (s, CH), 128.09 (s, CH), 153.62 (s, CH), 156.19 (s, CH), 156.93 (s, CH), 158.35 (s, CH), 158.46 (s, CH), 158.60 (s, CH) ppm. ESI-MS (CH_3CN, 20 V): m/z: 1748 [M^+].

New procedure for the synthesis of $[Mo_3S_4Cl_3(dmen)_3](BF_4)$: A mixture of $[Mo_3S_4(tu)_8(H_2O)]Cl_4{\cdot}4H_2O$ (0.150 g, 0.119 mmol), *N,N′*-dimethylethylenediamine (42 μL, 0.394 mmol) and CH_3CN (20 ml) was refluxed for 3 hours and allowed to cool to room temperature. Then, a freshly prepared 0.5 M in CH_3CN solution of $HBF_4{\cdot}$ether complex (0.95 mL, 0.477 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. After filtration, the green solution was taken to dryness, redissolved in CH_2Cl_2 and the precipitate of thiourea was eliminated by filtration. The solution was concentrated under reduced pressure and the desired product was precipitated by adding diethyl ether (75 mL). Finally, the green solid was separated by filtration and washed with diethyl ether to yield 0.08 g of an air stable product characterized as $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (77% yield).

Catalytic Activity Test

General procedure for the reduction of nitroarenes: A 4 mL glass vial containing a stirring bar was sequentially charged with the molybdenum catalyst (9.5 mg, 0.0050 mmol of $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$), nitrobenzene (10 μL, 0.097 mmol), *n*-hexadecane (15 μL; added as an internal standard) and 2 mL of methanol. Afterwards, the reaction vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to 20 bar and placed into an aluminum block, which was preheaated at 70ºC. After 18 h, the autoclave was cooled to room temperature and the hydrogen was released. Ethyl acetate (2 mL) was then added, and a sample was taken to be analyzed by GC. To determine the isolated yields of the anilines, the general procedure was scaled up by the factor of five, and no internal standard was added. After completion of the reaction, the mixture was purified by silica gel column chromatography (n-heptane/ethyl acetate mixtures) to give the corresponding anilines. For anilines obtained from the substrates 27 and 29 (Table 2), the isolation procedure was different because the products were insoluble in ethyl acetate. After the catalytic reaction, the mixture was taken to dryness and a small amount of CH_2Cl_2 was added to solve the catalyst. Then, the non-soluble aniline was recovered by filtration.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anilines • clusters • hydrogenation • molybdenum • nitroarenes • sulfides

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SUPPORTING INFORMATION

Chemoselective Hydrogenation of Nitroarenes Catalyzed by Molybdenum Sulphide Clusters

Elena Pedrajas, Iván Sorribes, Artem L. Gushchin, Yuliya A. Laricheva, Kathrin Junge, Matthias Beller* and Rosa Llusar*

1. General information.

2. Catalyst characterization.

Figure SI1. ^{1}H NMR spectrum of the diimino complex $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ ($[5](PF_6)$) in CD_2Cl_2.

Figure SI2. ^{13}C NMR spectrum of the diimino complex $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ ($[5](PF_6)$) in CD_2Cl_2.

Figure SI3. ESI mass spectrum of the diimino complex $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ ($[5](PF_6)$) in CH_3CN at 20 V.

3. Conditions optimization for the hydrogenation of nitrobenzene (1a) to aniline (2a).

Table SI1. Influence of the temperature in the hydrogenation of nitrobenzene (1a).

Table SI2. Influence of the pressure in the hydrogenation of nitrobenzene (1a).

Table SI3. Molybdenum sulphide-catalyzed hydrogenation of nitrobenzene (1a): Testing different solvents.

Table SI4. Catalyst loading variation on the catalytic hydrogenation of nitrobenzene (1a).

Figure SI4. ^{1}H NMR (a) and ESI mass (b) spectra of isolated aniline produced by hydrogenation of nitrobenzene using CD_3OD as solvent.

4. ESI mass spectra from monitoring of the nitrobenzene hydrogenation.

Figure SI5. ESI mass spectra from nitrobenzene hydrogenation monitoring at 90 and 240 min.: comparison with simulated peaks.

1. General Information.

General remarks: Starting complex $[Mo_3S_4(tu)_8(H_2O)]Cl_4{\cdot}4H_2O$ was prepared according to the published procedure.[1] All other reagents were obtained from commercial sources and used as received. Organic solvents were dried by standard methods before use.

Physical measurements

Elemental analyses were performed with a EuroEA3000 Eurovector analyzer. The ^1H NMR and ^{13}C NMR spectra of **[5]**(PF_6) were recorded with a Bruker Avance 500 spectrometer at room temperature. The shifts of the residual protons of the deuterated solvent (CD_2Cl_2) were used as an internal reference. Electrospray-ionization mass spectra were recorded with a Quattro LC (quadrupole-hexapole-quadrupole) mass spectrometer with an orthogonal Z-spray electrospray interface (Micromass, Manchester, UK). The cone voltage was set at 20 V unless otherwise stated, with CH_3CN as the mobile-phase solvent. Sample solutions were infused through a syringe pump directly connected to the ESI source at a flow rate of 10 μL/min, and a capillary voltage of 3.5 kV was used in the positive scan mode. Nitrogen was employed as the drying and nebulizing gas. Isotope experimental patterns were compared with theoretical patterns obtained by using the MassLynx 4.1 program.[2] The ^1H-NMR and ^{13}C-NMR spectra of the isolated anilines were recorded on a Bruker AV 300 or Bruker AV 400 spectrometer. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) in Hz. For ^1H-NMR all chemical shifts are reported relative to tetramethylsilane (δ 0.0 ppm in $CDCl_3$ or DMSO) or d-solvent peaks (δ 77.16 ppm $CDCl_3$; δ 39.52 ppm DMSO) for ^{13}C-NMR. All measurements were carried out at room temperature unless otherwise stated. The GC yields were determined by GC-FID using *n*-hexadecane as an internal standard. GC-FID was performed on a HP5890 series GC System using Argon as a

carrier gas. Mass determination was carried out on a GC-Mass Agilent 5973 Network equipped with a mass selective detector.

2. Catalyst characterization.

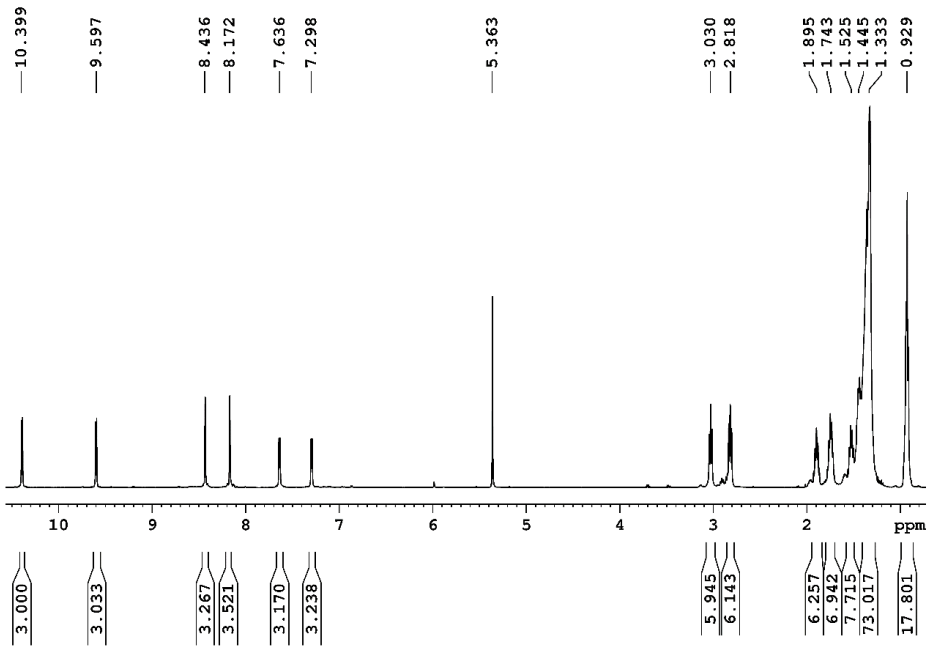


Figure SI1. ^{1}H NMR spectrum of the diimino complex $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ ([**5**](PF_6)) in CD_2Cl_2.

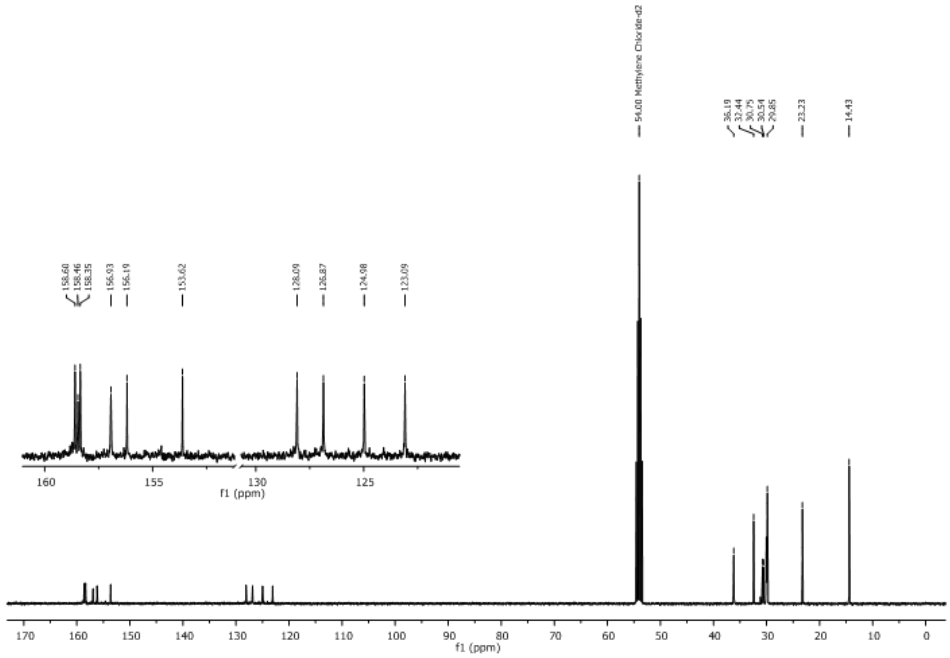


Figure SI2. ^{13}C NMR spectrum of the diimino complex $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ ([**5**](PF_6)) in CD_2Cl_2.

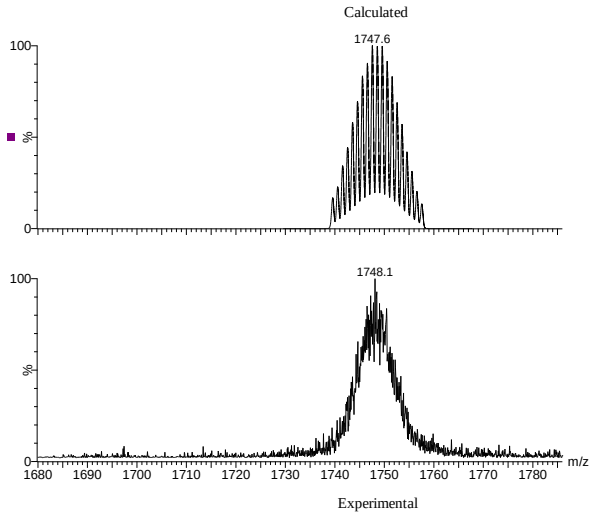
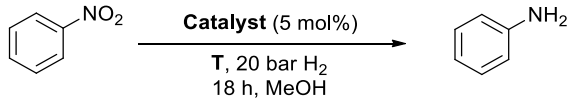


Figure SI3. ESI mass spectrum of the diimino complex $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ ([**5**](PF_6)) in CH_3CN at 20 V.

3. Conditions optimization for the hydrogenation of nitrobenzene (1a) to aniline (2a).

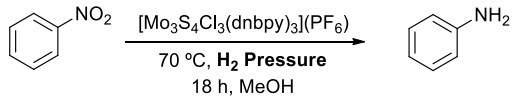
Table SI1. Influence of the temperature in the hydrogenation of nitrobenzene (**1a**).[a]



Entry	Catalyst	Temperature (ºC)	Conversion. (%)[b]	Yield (%)[b]
1	**[5]**(PF_6)	100	>99	95
2	**[6]**(BF_4)	100	>99	>99
3	**[5]**(PF_6)	80	>99	98
4	**[6]**(BF_4)	80	>99	>99
5	**[5]**(PF_6)	70	>99	>99
6	**[6]**(BF_4)	70	>99	>99
7	**[5]**(PF_6)	60	93	93
8	**[6]**(BF_4)	60	81	81

[a]Reaction conditions: nitrobenzene (0.1 mmol), 20 bar H_2, catalyst (5 mol%), MeOH (2 mL), 18 h. [b]Determined by GC analysis using *n*-hexadecane as an internal standard.

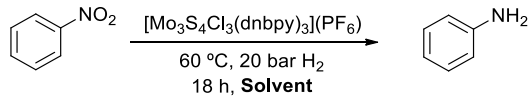
Table SI2. Influence of the pressure in the hydrogenation of nitrobenzene (**1a**).[a]



Entry	Pressure (bar)	Conversion. (%)[b]	Yield (%)[b]
1	20	>99	>99
2	15	89	89
3	10	77	77
4[c]	0	0	0

[a] Reaction conditions: nitrobenzene (0.1 mmol), catalyst (5 mol%), MeOH (2 mL), 18 h, 70 ºC. [b] Determined by GC analysis using *n*-hexadecane as an internal standard. [c] Experiment carried out in the absence of H_2.

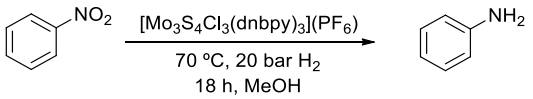
Table SI3. Molybdenum sulphide-catalyzed hydrogenation of nitrobenzene (**1a**): Testing different solvents.[a]



Entry	Solvent	Conversion (%)[b]	Yield (%)[b]
1	MeOH	93	93
2	EtOH	60	60
3	^{i}PrOH	27	27
4	THF	1	1
5	MeCN	25	25
6	Toluene	0	0
7	1,4-Dioxane	0	0

[a]Reaction conditions: nitrobenzene (0.1 mmol), 20 bar H_2, catalyst (5 mol%), Solvent (2 mL), 18 h, 60 ºC. [b]Determined by GC analysis using *n*-hexadecane as an internal standard.

Table SI4. Catalyst loading variation on the catalytic hydrogenation of nitrobenzene (**1a**).[a]



Entry	$[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ (mol %)	Conversion. (%)[b]	Yield (%)[b]
1	-	-	-
2	1	4	4
3	2	31	31
4	3	63	61
5	4	>99	>99
6	5	>99	>99

[a]Reaction conditions: nitrobenzene (0.1 mmol), 20 bar H_2, catalyst (x mol%), MeOH (2 mL), 18 h, 70 ºC. [b]Determined by GC analysis using *n*-hexadecane as an internal standard.

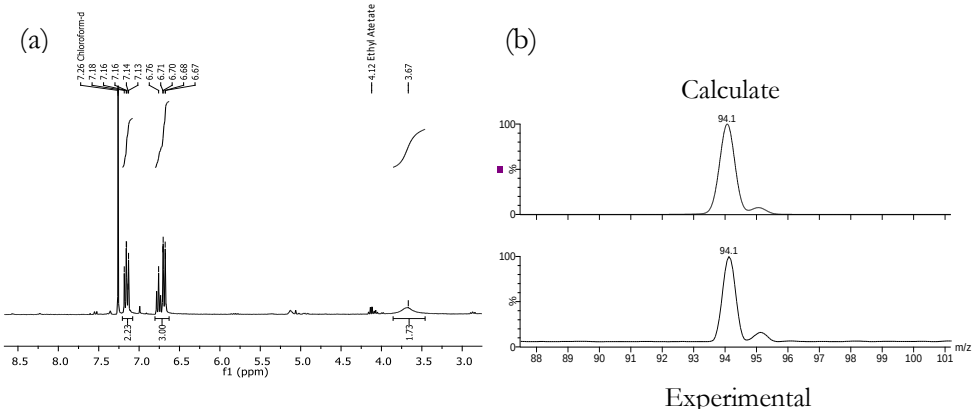


Figure SI4. ^{1}H NMR (a) and ESI mass (b) spectra of isolated aniline produced by hydrogenation of nitrobenzene using CD_3OD as solvent.

4. ESI mass spectra from monitoring of the nitrobenzene reaction.

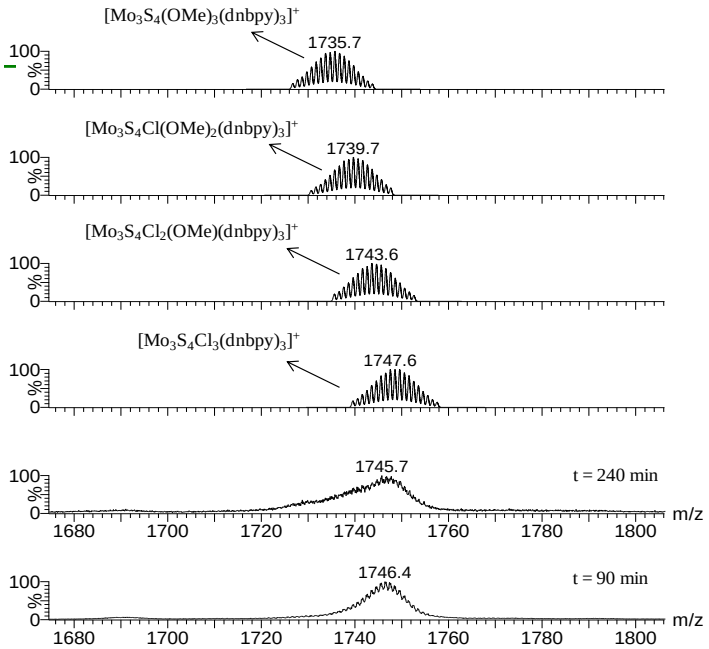
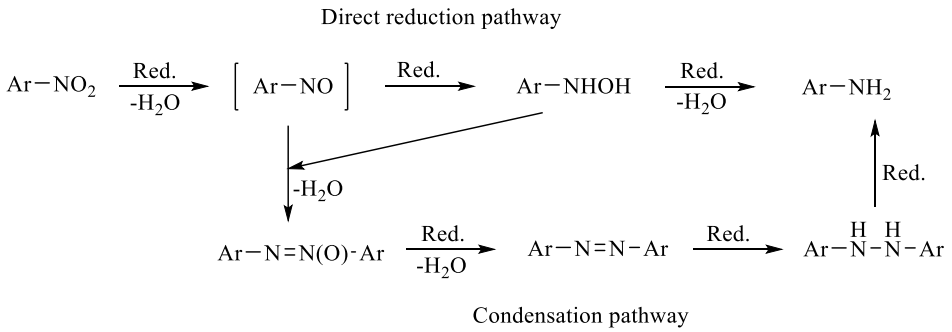


Figure SI5. ESI mass spectra from nitrobenzene hydrogenation monitoring at 90 and 240 min.: comparison with simulated peaks.

5. Reaction pathway investigation.



Scheme SI1. Possible reaction pathways for the hydrogenation of nitrobenzene (**1a**) to aniline (**2a**).

Table SI5. Hydrogenation of possible reaction intermediates for the hydrogenation of nitrobenzene (**1a**).[a]

Entry	Substrate	Conversion. (%)[b]	Yield (%)[b]
1	Azoxybenzene (Ph-NO=N-Ph)	>99	93
2	Azobenzene (Ph-N=N-Ph)	>99	97
3	Nitrosobenzene (Ph-NO)	>99	85
4	N-Phenylhydroxylamine (Ph-NHOH)	>99	94

[a]Reaction conditions: substrate (0.1 mmol), 20 bar H_2, catalyst (20 mol%), MeOH (2 mL), 18 h, 70 ºC. [b]Determined by GC analysis using *n*-hexadecane as an internal standard.

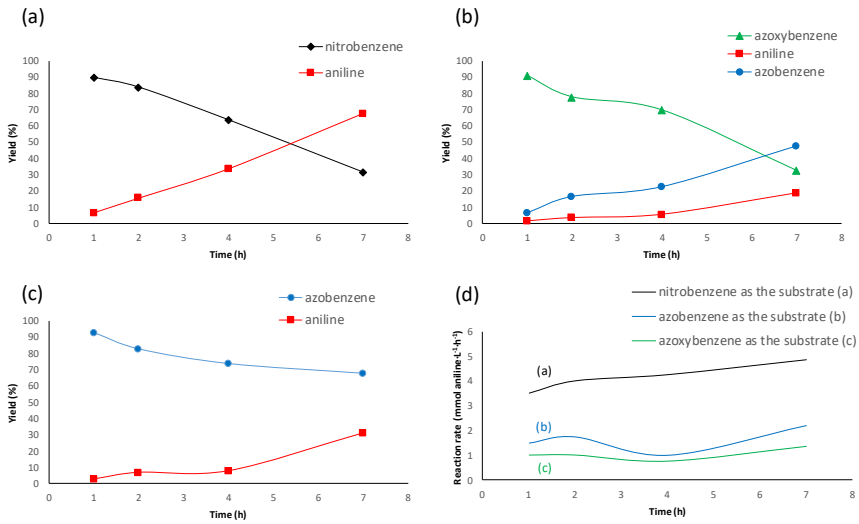
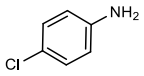
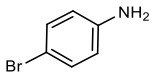


Figure SI6. The yield-time curves of nitrobenzene (a), azoxybenzene (b), azobenzene (c) and their reaction rate (d). Reaction conditions: substrate (0.1 mmol), 20 bar H_2, catalyst (5 mol %), MeOH (2 mL), 18 h, 70 ºC.

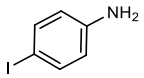
6. Characterization data of isolated products.



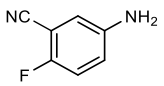
4-chloroaniline[3]: isolated yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.07 (m, 2H), 6.63-6.58 (m, 2H), 3.48 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.03, 129.24, 123.30, 116.37; MS (EI): *m/z* (rel. int.) 127.



4-bromoaniline[3]: isolated yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.13 (m, 2H), 6.51-6.46 (m, 2H), 3.58 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.54, 132.14, 116.83, 110.33; MS (EI): *m/z* (rel. int.) 172.

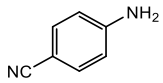


4-iodoaniline[3]: isolated yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.38 (m, 2H), 6.49-6.44 (m, 2H), 3.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.19, 138.02, 117.40, 79.47; MS (EI): *m/z* (rel. int.) 219.

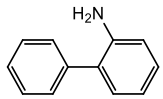


5-amino-2-fluorobenzonitrile[4]: isolated yield: 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02-6.95 (m, 1H), 6.87-6.81 (m, 2H), 3.76 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [158.31, 155.01 (d, $^{1}J_{C\text{-}F}$ = 249.2 Hz)], [143.20, 143.16 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz)], [121.27,

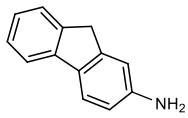
121.18 (d, $^{3}J_{C\text{-}F}$ = 7.2 Hz)], 117.76, [117.33, 117.06 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz)], [115.09, 114.45 (d, $^{2}J_{C\text{-}F}$ = 48.5 Hz)], [101.53, 101.34 (d, $^{3}J_{C\text{-}F}$ = 14.3 Hz)]; MS (EI): *m/z* (rel. int.) 136.



4-aminobenzonitrile[3]: isolated yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 6.66-6.61 (m, 2H), 4.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.59, 133.86, 120.30, 114.50, 100.04; MS (EI): *m/z* (rel. int.) 118.

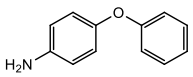


2-aminobiphenyl[5]: isolated yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.44 (m, 4H), 7.37 (tdd, *J* = 5.3, 4.0, 2.6 Hz, 1H), 7.21-7.15 (m, 2H), 6.86 (td, *J* = 7.4, 1.2 Hz, 1H), 6.79 (dd, *J* = 7.8, 0.7 Hz, 1H), 3.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.61, 139.64, 130.56, 129.20, 128.92, 128.61, 127.74, 127.27, 118.75, 115.71; MS (EI): *m/z* (rel. int.) 169.

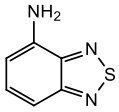


2-aminofluorene[3]: isolated yield: 91%.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.25 – 7.17 (m, 1H), 7.11 – 7.05 (m, 1H), 6.73 – 6.70 (m, 1H), 6.57 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.67 (s, 2H); ^{13}C

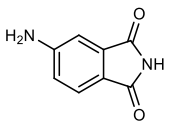
NMR (75 MHz, $CDCl_3$) δ 145.83, 145.19, 142.31, 142.19, 132.97, 126.68, 125.12, 124.81, 120.69, 118.63, 114.01, 111.84, 36.86; MS (EI): *m/z* (rel. int.) 181.



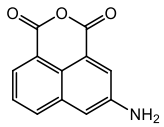
4-phenoxyaniline[6]: isolated yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.17 (m, 2H), 6.96-6.90 (m, 1H), 6.87-6.84 (m, 2H), 6.81-6.77 (m, 2H); 6.62-6.57 (m, 2H), 3.32 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.00, 148.71, 142.76, 129.64, 122.18, 121.26, 117.33, 116.39; MS (EI): *m/z* (rel. int.) 185.



4-Amino-2,1,3-benzothiadiazole[3]: isolated yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 2H), 6.59 (dd, *J* = 6.7, 1.4 Hz, 1H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.84, 147.85, 138.98, 131.30, 110.09, 106.69; MS (EI): *m/z* (rel. int.) 151.



5-aminoisoindoline-1,3-dione: isolated yield: 95%. ^{1}H NMR (300 MHz, DMSO-D6) δ 10.72 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 6.78 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.40 (s, 2H); ^{13}C NMR (75 MHz, DMSO-D6) δ 169.73, 169.39, 154.88, 135.50, 124.69, 117.92, 116.83, 106.64; MS (EI): *m/z* (rel. int.) 162.



5-aminobenzo[de]isochromene-1,3-dione[7]: isolated yield: 99%. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.13-8.06 (m, 2H), 7.95 (d, *J* = 2.3 Hz, 1H), 7.64 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 6.11 (s, 2H); ^{13}C NMR (75 MHz, DMSO-D6) δ 161.06, 160.94, 148.19, 133.64, 132.60, 127.32, 127.16, 123.08, 122.89, 119.30, 118.51, 112.64; MS (EI): *m*/*z* (rel. int.) 213.

7. References.

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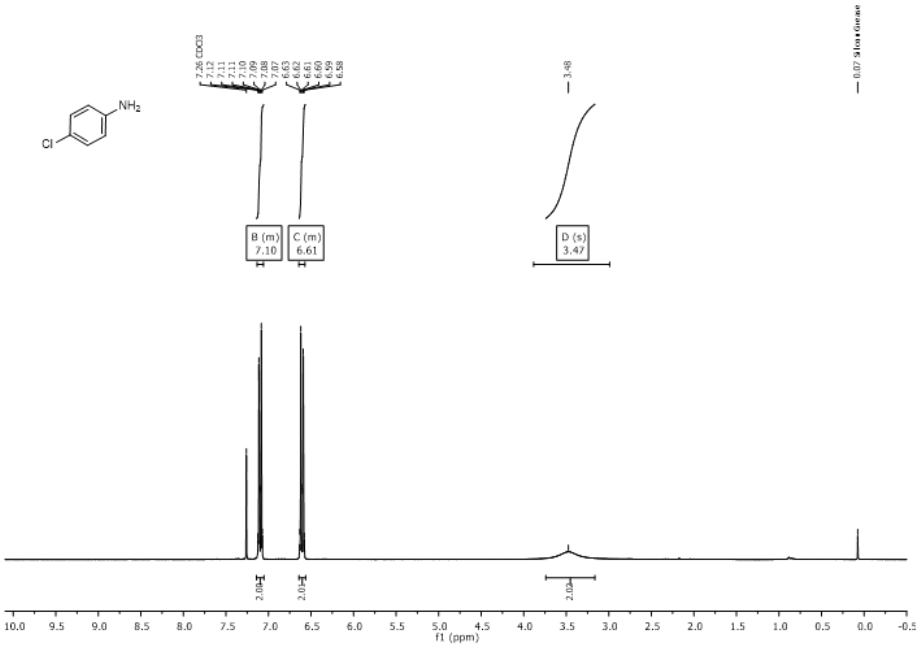
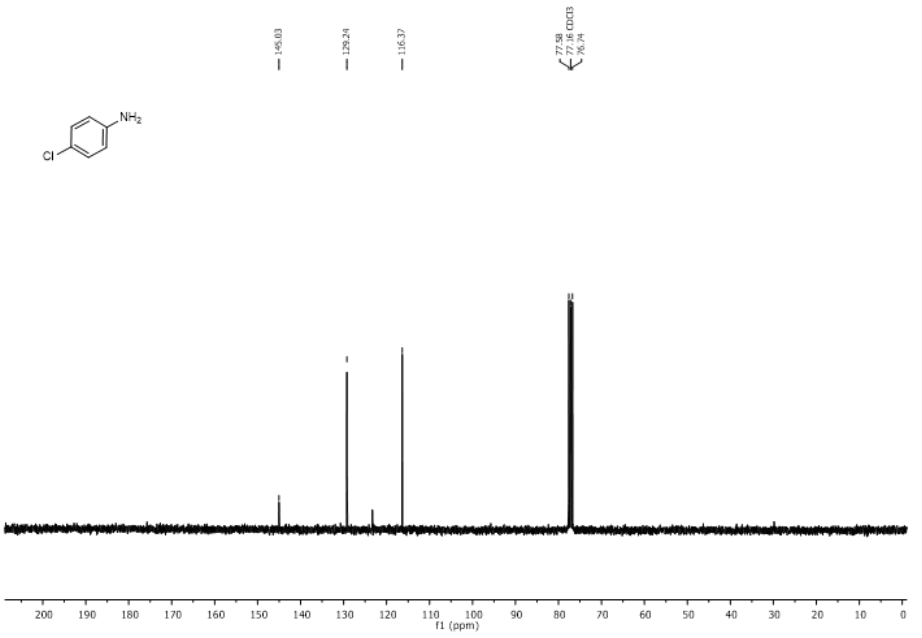
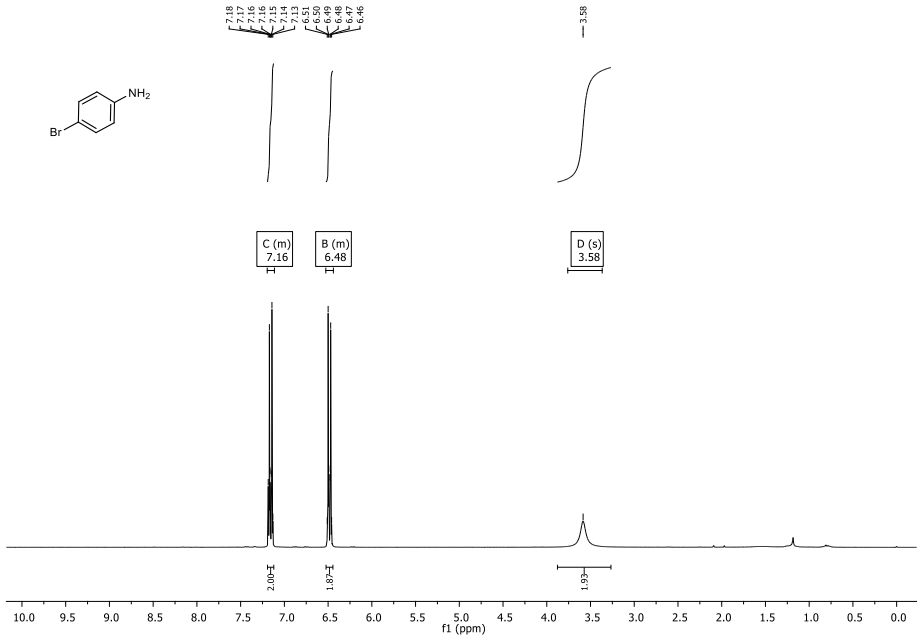
8. ^{1}H NMR and ^{13}C NMR spectra of isolated products.






7.18
7.17
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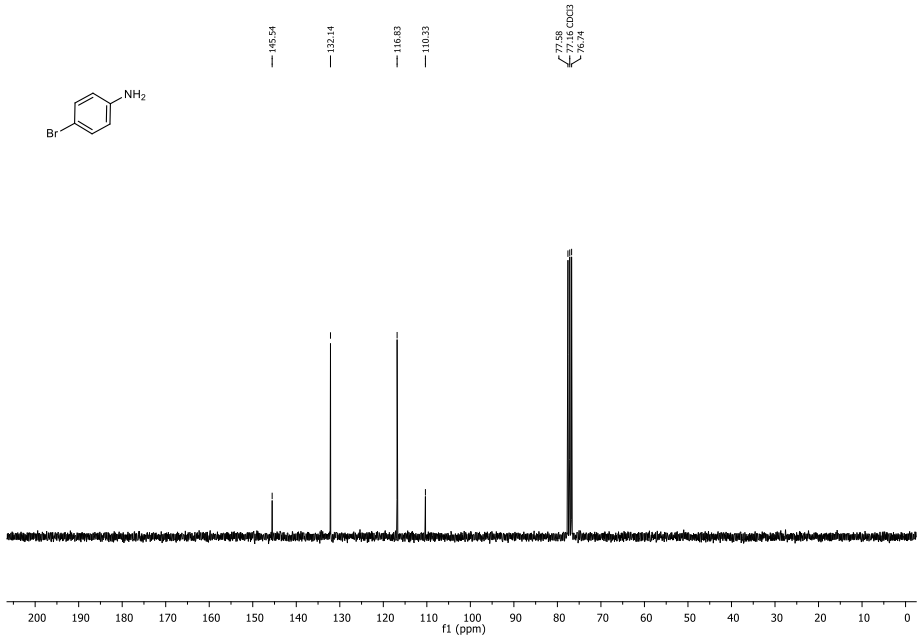
7.16
7.15
7.14
7.13
6.51
6.50
6.49
6.48
6.47
6.46
3.58
NH2
Br
C (m)
7.16
B (m)
6.48
D (s)
3.58
2.00
1.87
1.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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132.14
116.83
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77.58
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NH2
Br
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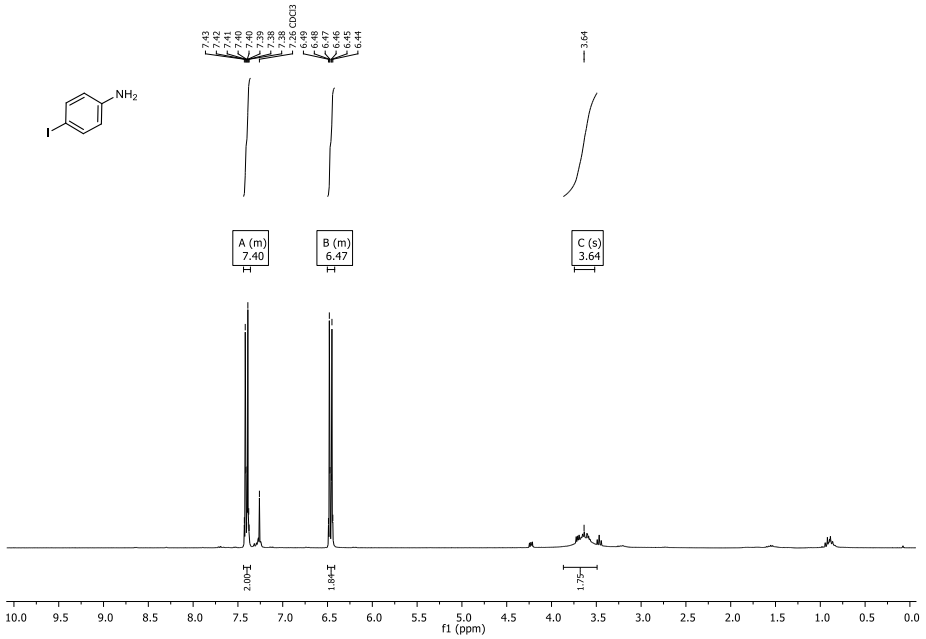
f1 (ppm)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7.42
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7.40
7.40
7.39
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7.26 CDCl3
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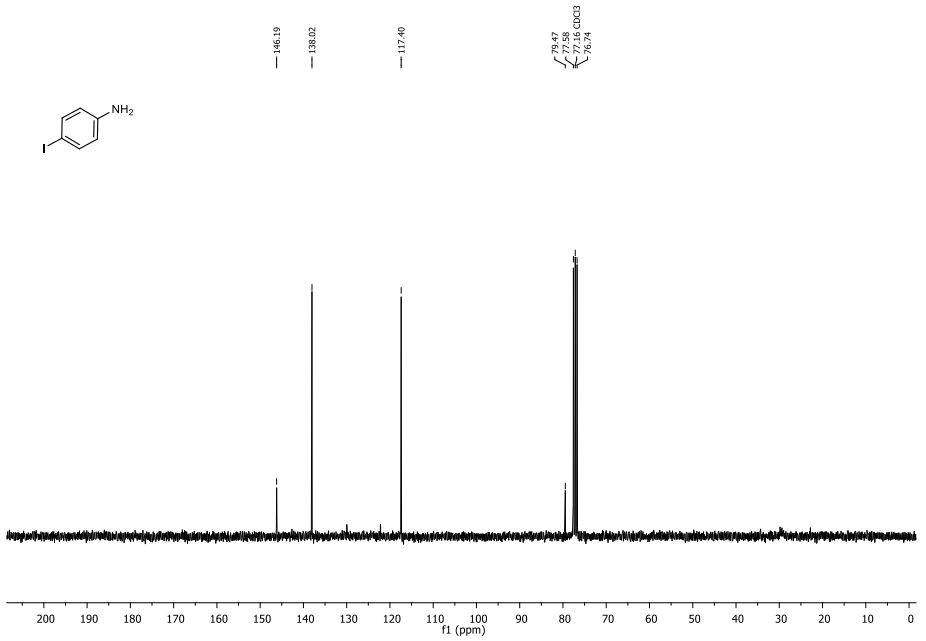
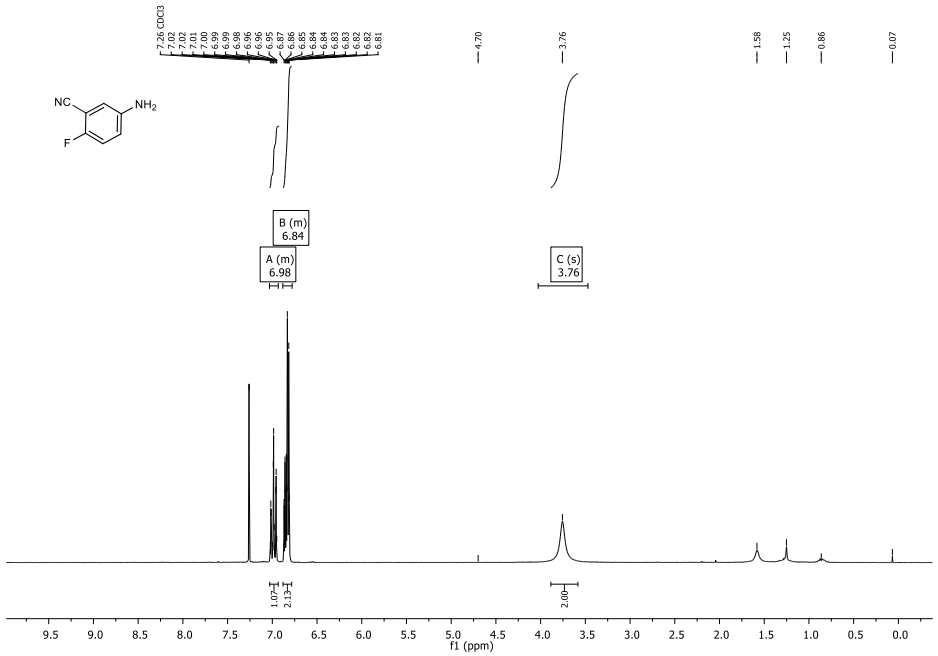
6.48
6.47
6.46
6.45
6.44
3.64
NH2
I
A (m)
7.40
B (m)
6.47
C (s)
3.64
2.00
1.84
1.75
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


146.19
138.02
117.40
79.47
77.58
77.16 CDCl3
76.74
NH2
I
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26 CDCl3
7.02
7.01
7.00
6.99
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6.96
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C (s)
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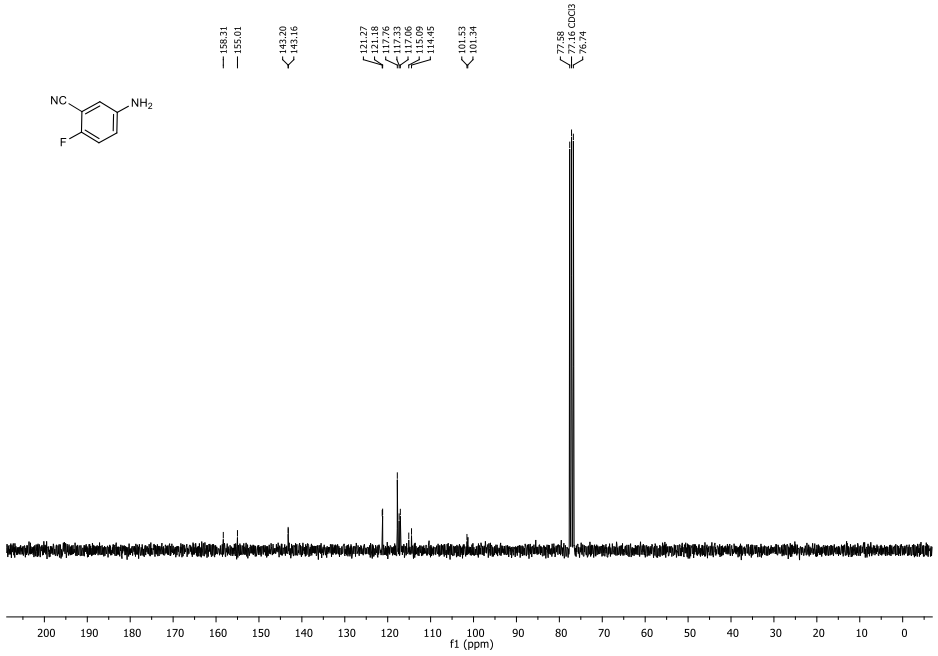
f1 (ppm)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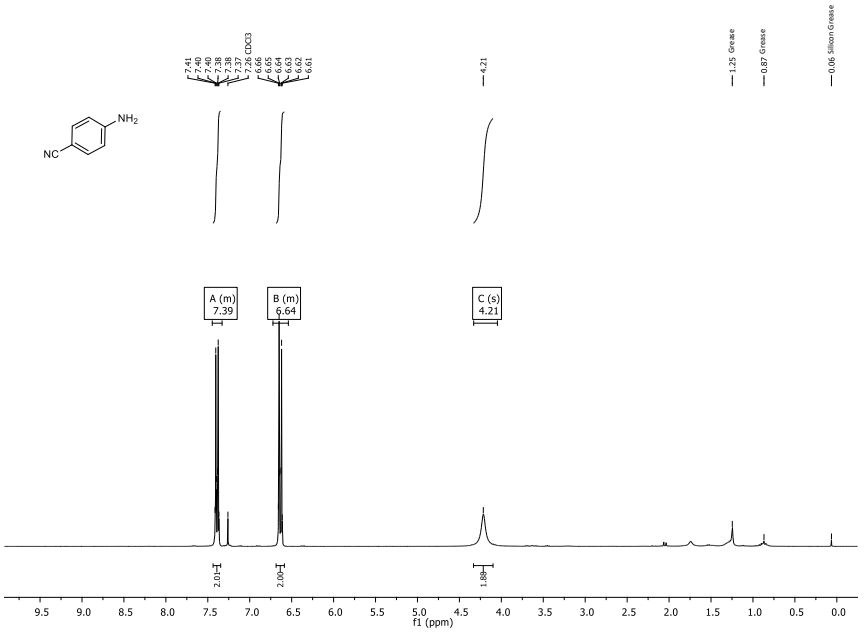
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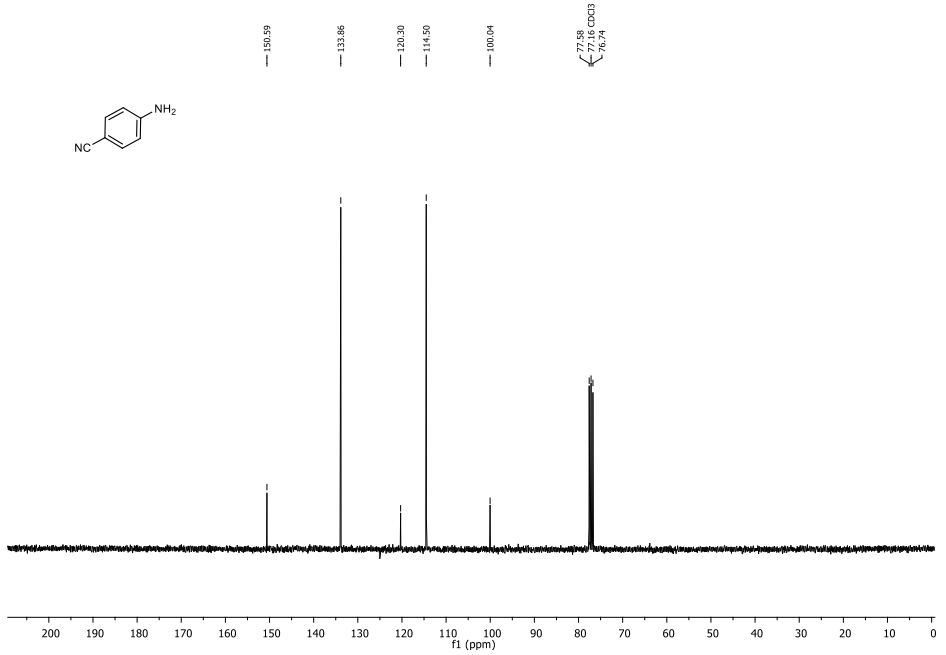
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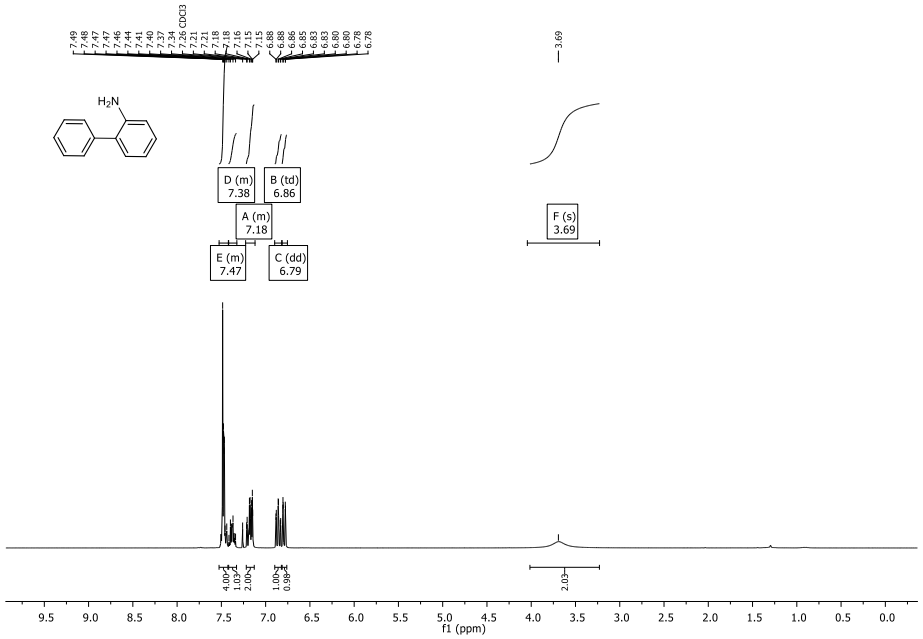
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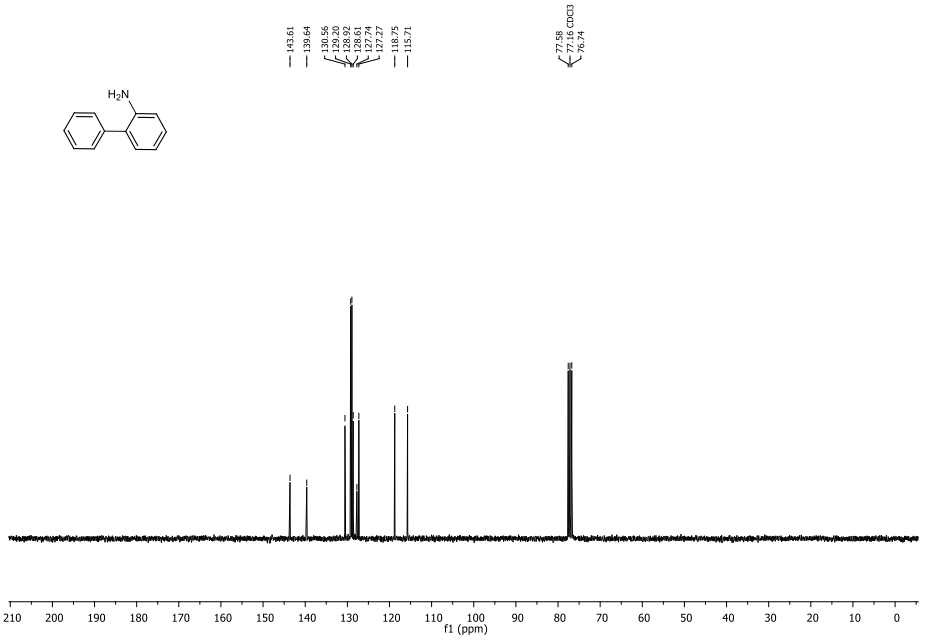
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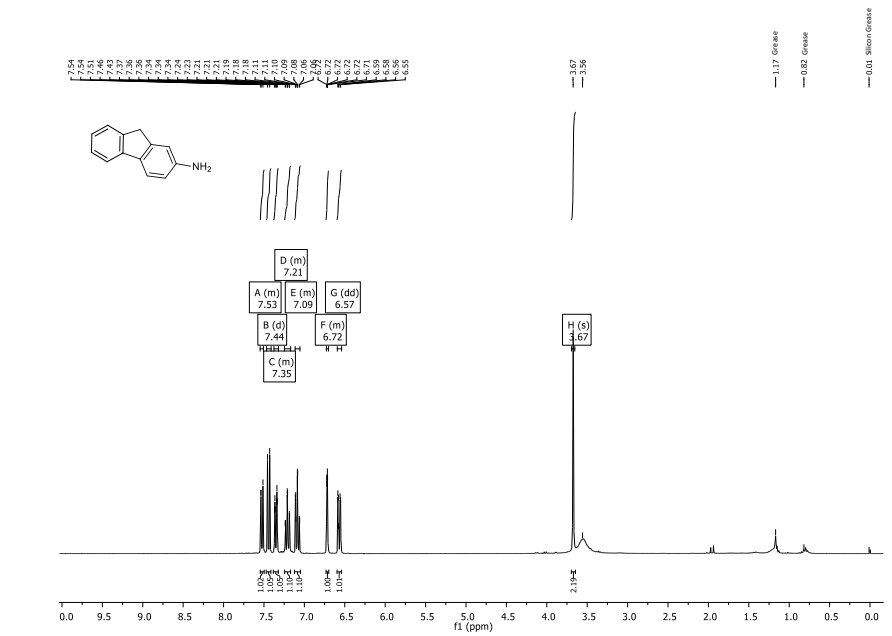
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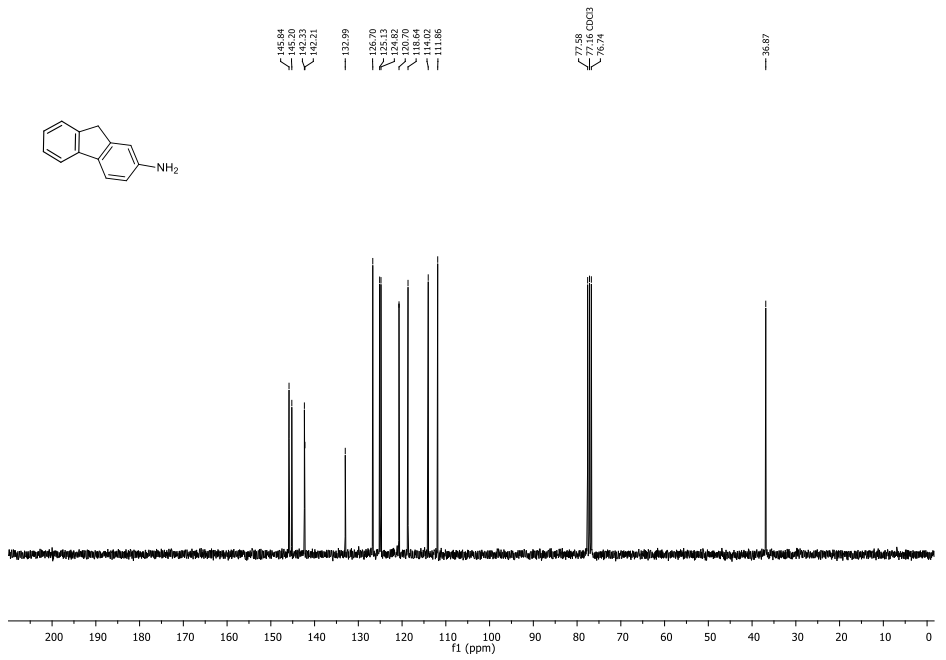
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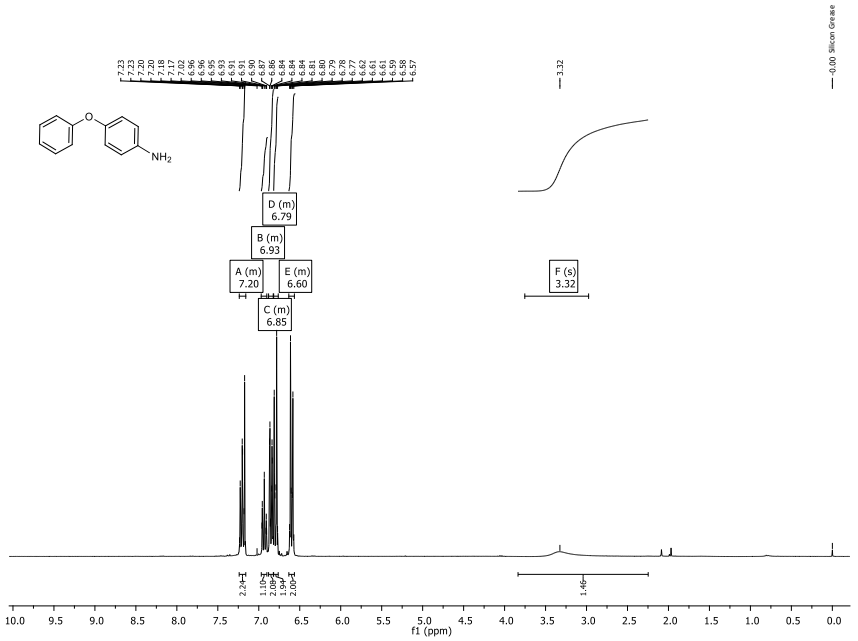
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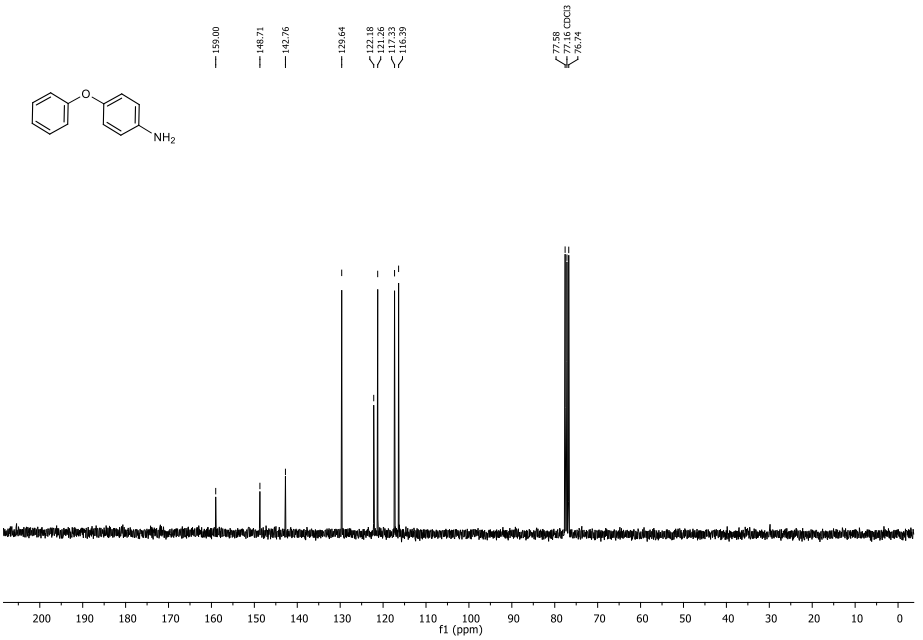
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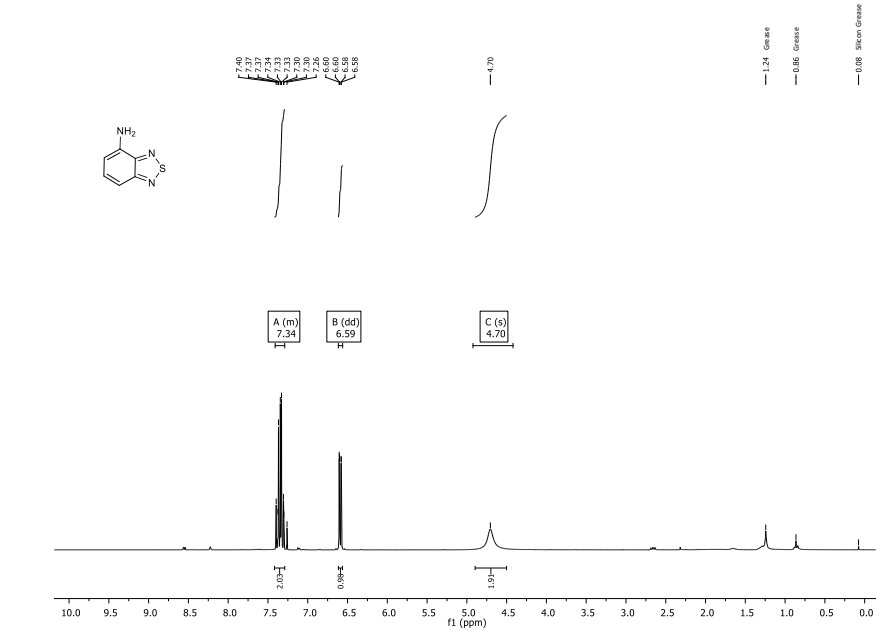
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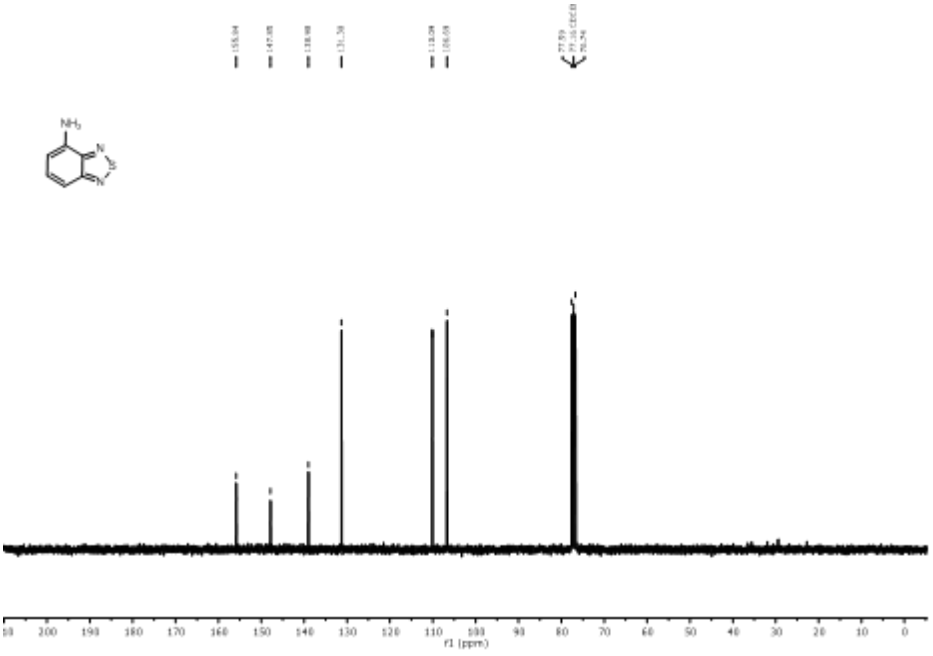
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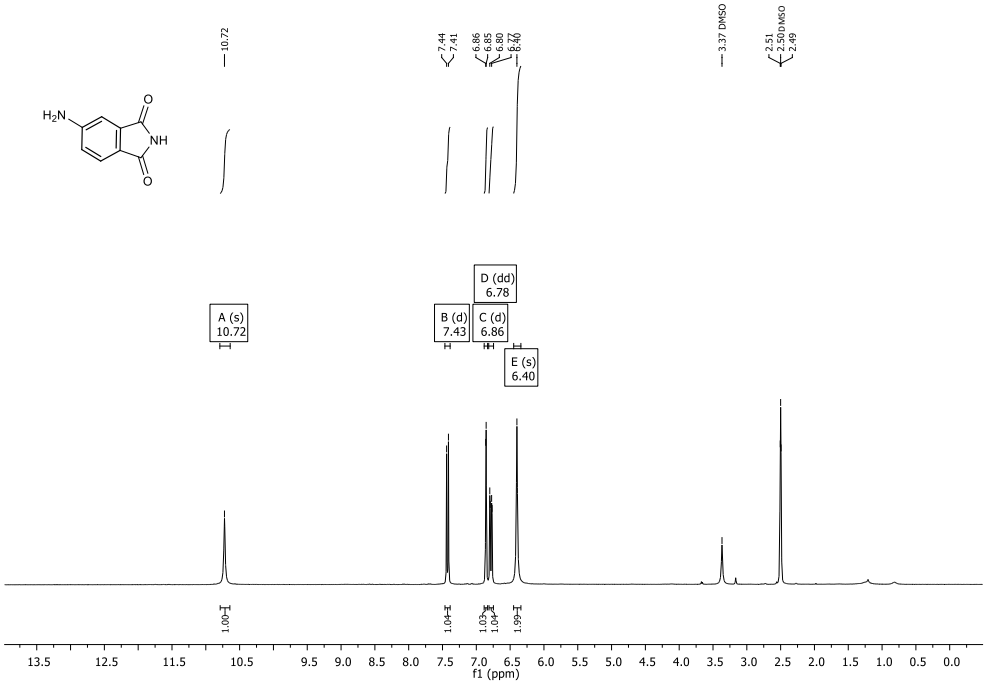
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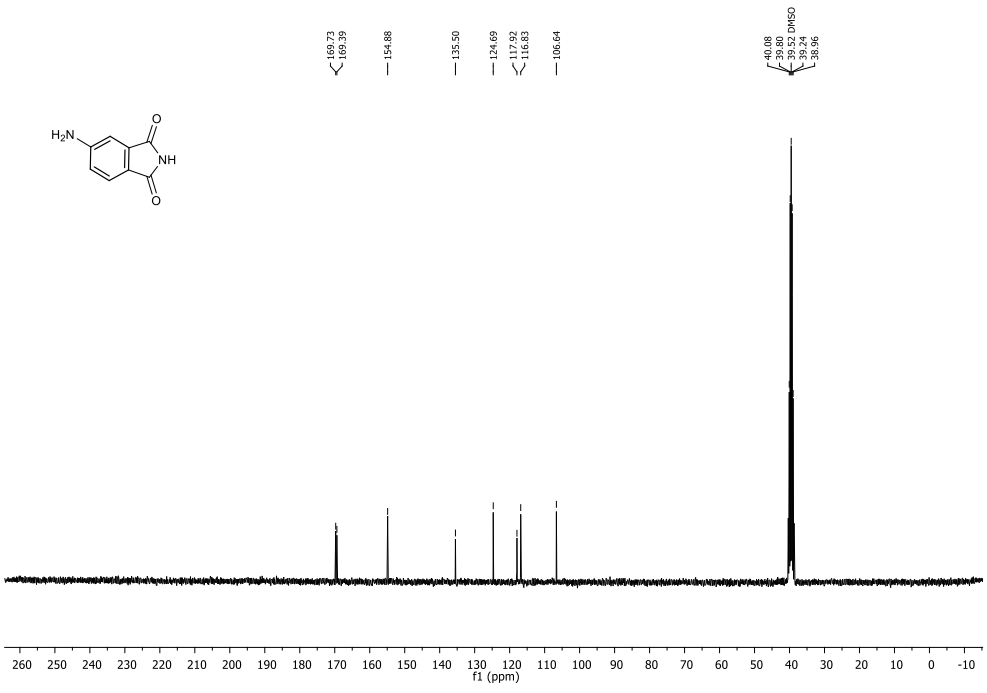
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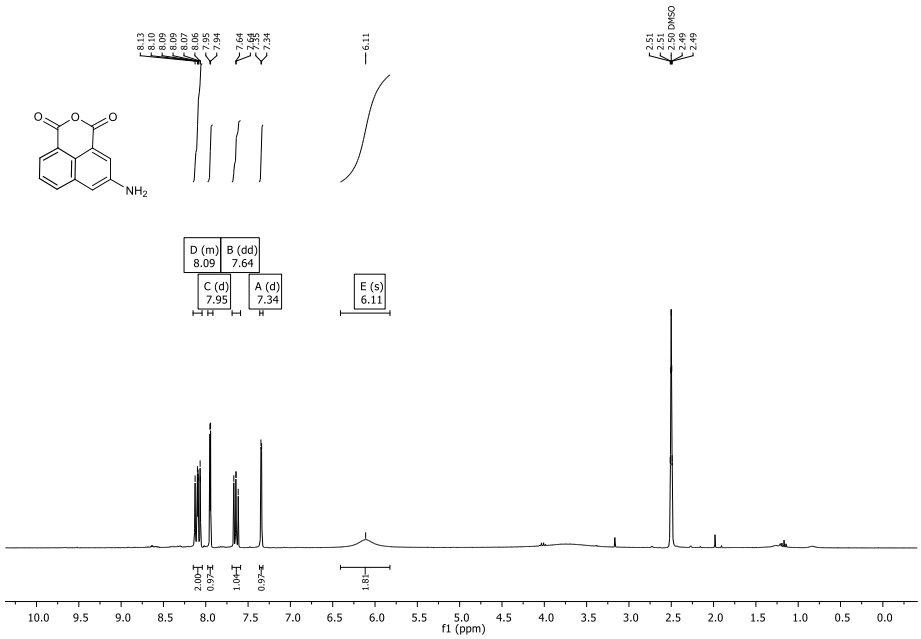
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E (s) 6.11
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10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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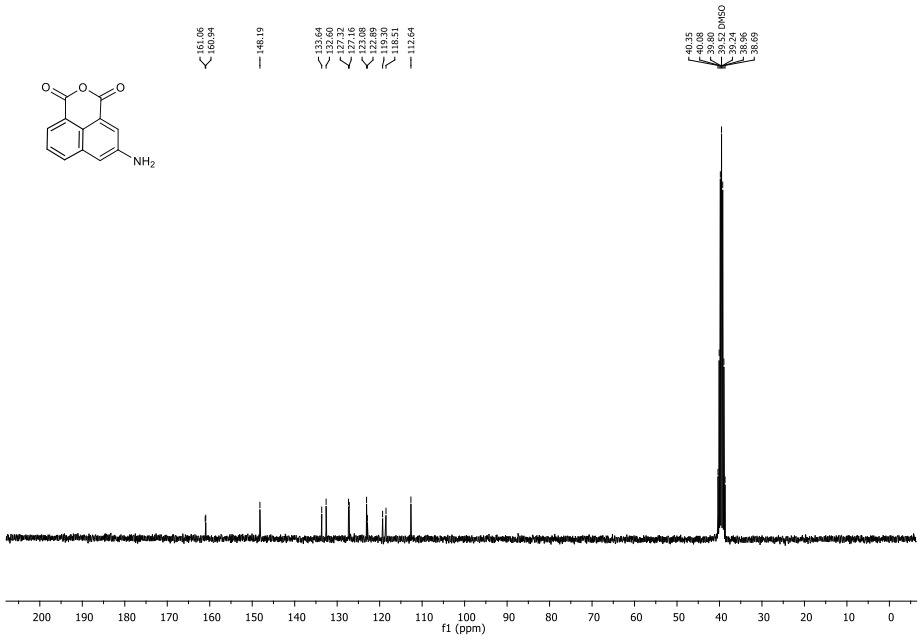
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39.24
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38.69
NH2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

5

Selective reductive amination of aldehydes from nitro compounds catalyzed by molybdenum sulfide clusters

5. Selective reduction amination of aldehydes from nitro compounds catalyzed by molybdenum sulfide clusters
    5.1. Manuscript
    5.2. Supporting Information

"Un experto es una persona que ha cometido todos los errores que pueden hacerse en un campo muy estrecho."

Niels Bohr

Selective Reduction Amination of Aldehydes from Nitro Compounds Catalyzed by Molybdenum Sulfide Clusters

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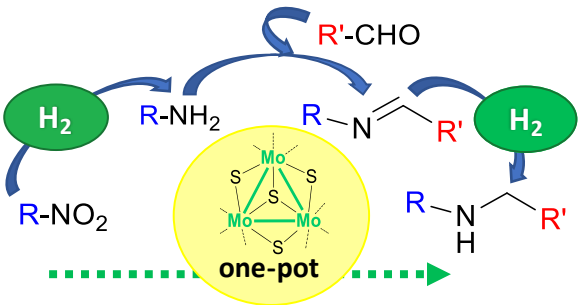
*(Accepted with revisions in **Green Chemistry**)*



One-pot selective synthesis of secondary amines catalyzed by a well-defined Mo_3S_4 cluster using hydrogen as benign reductant.

Abstract

Secondary amines are selectively obtained from low value starting materials using hydrogen and a non-noble metal based catalyst. Reductive amination of aldehydes from nitroarenes or nitroalkanes is efficiently catalyzed by a well-defined diamino molybdenum sulfide cluster in a one-pot homogeneous reaction. The integrity of the molecular cluster catalyst is preserved along the process.

Introduction

Amines are the most important building blocks employed in modern medicinal chemistry.[1] Secondary amines are regularly prepared by alkylation or reductive amination of the parent amine through transition metal, typically precious metals, catalyzed reactions.[2,3] In the last years, the catalytic alkylation of amines with alcohols under hydrogen-borrowing conditions[4] as well as the catalytic reductive amination of carbonyl compounds using hydrogen as reductant have been proposed as environmentally friendly procedures to produce *N*-substituted amines.[5]

An actual challenge in catalysis research is to take low value starting materials and convert them to a high value product using non-toxic earth abundant materials through an atom efficient procedure. Nitro compounds are an economic feedstock to provide primary amines and its use in reductive amination processes is highly attractive since it does not require prior isolation of the amine. Our groups have recently shown that well-defined Mo_3S_4 cuboidal clusters are efficient catalysts for the chemoselective reduction of nitroarenes to anilines using different reducing agents.[6–8] Interestingly, the diamino cluster of formula $[Mo_3S_4Cl_3(dmen)_3]^+$ (dmen = *N,N'*-dimethylethylenediamine), depicted in Figure 1, performs this transformation under mild conditions and using molecular hydrogen, the most "green" and least expensive reducing agent.[6] On this basis, we became interested on its use as catalyst for the related reductive amination of aldehydes with nitroarenes and nitroalkanes to generate secondary amines in a straightforward manner.

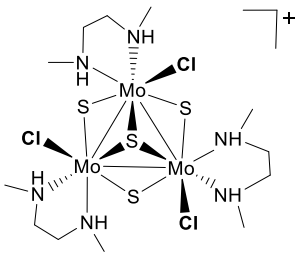


Figure 1. Structure of the $[Mo_3S_4Cl_3(dmen)_3]^+$ cluster catalyst.

Domino catalytic transformations starting from nitroarenes and carbonyl compounds directed towards the preparation of *N*-alkylated aryl amines are not so common and they are usually done in heterogeneous phase using palladium, platinum, rhodium or gold nanocatalysts.[9–16] *N*-alkylation of nitroarenes with aldehydes catalyzed by palladium operates under ambient hydrogen pressure at room temperature when alcohols are used as solvents. However, formation of byproducts such as benzylalcohol and toluene derivatives limits the selectivity of the process. Several cost effective carbon-supported catalysts based on nanostructured Fe_2O_3 and Co-Co_3O_4 doped with graphene layers (Fe_2O_3/NGr@C and Co-Co_3O_4/NGr@C, respectively) have also been recently developed by some of us for the tandem reductive amination between nitro compounds and carbonyl compounds using hydrogen as reductant.[17–19] In general, these heterogeneous processes employing non-noble metals require more demanding conditions (110-170 ^oC and 50-70 bar H_2) and contrary to general assumption that anhydrous conditions favor reductive aminations, water has a positive influence on the reaction. Lanthanide Metal Organic Frameworks have also proved to be active catalysts for the tandem reductive amination of nitrobenzene with heptanal to produce *N*-heptylaniline in moderate yields.[20]

Although heterogeneous catalysts are usually preferred for most industrial applications, molecularly defined complexes are still an attractive approach in

catalysis due to their higher selectivity and easy modification. To our knowledge, the only examples of homogeneous catalysts capable to afford secondary amines from nitroarenes and aldehydes in the presence of hydrogen in a tandem fashion were reported by Corma's group. The iridium (2-aminoterephtalato) complex is able to produce *N*-benzylaniline in 66% yield after full conversion of nitrobenzene under 6 bar of H_2 pressure and 100 ^{0}C, while the pincer (NHC)NNRu complex affords 86% conversion and 25% yield under similar conditions (80 ^{0}C and 5 bar H_2).[21,22] Remarkably, immobilization of these molecular complexes in mesoporous silica or MOF architectures combines the catalytic power of the iridium or ruthenium complex with that of the support enhancing both conversion and selectivity.

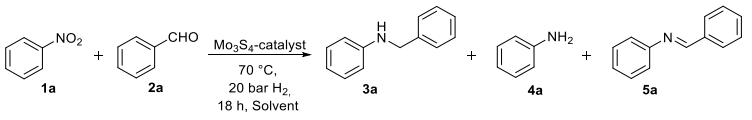
Homogeneous catalysis by well-defined metal cluster complexes offers the possibility of performing complex transformation similar to those observed in heterogeneous phase, which are known to be difficult to trace and control. Herein, we report the first homogeneous catalyst based on non-noble metals for the clean and atom efficient *N*-alkylation of amines starting from nitro compounds and aldehydes using molecular hydrogen as a benign reducing agent. The catalyst, a diamino cuboidal molybdenum sulfide cluster, is highly selective and preserves its integrity during the process.

Results and discussion

An initial evaluation of the $[Mo_3S_4Cl_3(dmen)_3]^+$ catalyst performance on the model reaction of nitrobenzene (**1a**) with benzaldehyde (**2a**) was realized using different solvents motivated by the already established solvent influence on the reactants conversion and products selectivity.[17,19] For this study, we have tentatively chosen the optimum reaction conditions used for the hydrogenation of nitroarenes to anilines applying this molybdenum-based complex (18 h at 70 °C under 20 bar H_2 and 5 mol% of catalyst) and 1.2 equivalents of **2a** has been added to the reaction mixture.[6] While methanol appears as an optimum solvent for the hydrogenation of

nitroarenes, the best yield towards the formation of the *N*-benzylaniline (**3a**) has been obtained in THF (Table 1, entries 1-3). When molecular sieves are added to remove water from the reaction mixture and tentatively shift the equilibrium towards the in situ generated imine, conversion of **1a** halved and no secondary amine **3a** is formed (Table 1, entry 4). Surprisingly, similar reactivity is observed in THF-H_2O mixtures (Table1, entries 5 and 6). Thus, traces of water, approximately between 150 and 1500 ppm, are needed to achieve a quantitative formation of **3a**, while an excess of water has a detrimental effect on the reaction outcome (Table 1, entry 4). These results suggest a direct implication of the water molecules in the reaction mechanism. The beneficial effect of controlled amount of water in the reductive *N*-alkylation of amines is not unprecedented.[23] In contrast, larger amounts of water, up to 50%, are tolerated in the tandem reactions of nitro compounds to secondary amines catalyzed by Co-Co_3O_4/NGr@C and Fe_2O_3/NGr@C catalysts in THF.[17–19] In this last case, water addition is believed to promote hydrophobic association of aldehydes and amines as well as suppress catalysts poisoning.[24]

Table 1. Influence of the solvent in the reductive amination of nitrobenzene with benzaldehyde.



Entry [a]	Solvent	Conv. [%][b]	Yield [%][b]		
			3a	**4a**	**5a**
1	1,4-Dioxane	31	0	7	22
2	CH_3OH	99	74	23	0
3	THF (150-1500 ppm of H_2O)	>99	99	0	0
4	THF (molecular sieves)	50	0	18	30
5	THF-H_2O (10:1)	47	0	36	11
6	THF-H_2O (5:1)	14	0	11	2

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), H_2 (20 bar), catalyst (5 mol %), solvent (2 mL), 18 h, 70 ºC. [b] Determined by GC analysis using hexadecane as an internal standard.

Next, optimization of the temperature, hydrogen pressure and catalyst loading was addressed (Tables SI1, SI2 and SI3). Full conversion of 1a with a quantitative yield of 3a (>99%) occurs at 70 ^{0}C, 20 bar of hydrogen pressure and 5 mol% of catalyst loading within 18 hours. In contrast, partial conversion of 1a (48%) with only scarce formation of 3a (7% yield) is achieved after 4 h. Then, longer reaction times are needed for the reduction of the imine intermediate, which is in good agreement with the general tendency that imine hydrogenation is regarded as the rate-determining step in the reductive amination sequence. It shoud be noted that when aldehydes were replaced by ketones, the reaction stopped at the aniline formation stage and no traces of the iminium ion or the secondary amine could be detected.

Our recent works on the catalytic reduction of nitroarenes to aniline derivatives mediated by Mo_3S_4-based clusters decorated with diphosphino, diamino or diimino ligands show no fragmentation of the cluster core during the first stage of this tandem process.[6–8] Here, a color change, from green to brown, occurs during the catalytic process due to the basicity increase caused by the amine generation. However, analysis of the reaction mixture by electrospray ionization mass spectrometry (ESI-MS), shows a single peak at m/z = 786.9, associated to the pseudomolecular $[Mo_3S_4Cl_3(dmen)_3]^+$ ion on the basis of the m/z value and its characteristic isotopic pattern (Figure SI1). Additionally, cluster integrity was further confirmed by ^{1}H NMR spectroscopy (Figure SI2). Therefore, the integrity of the cluster core is also preserved during the reductive amination stage. In addition, catalyst recycling in the model reaction after recovering the catalyst by evaporating, washing and drying the reaction mixture, shows full conversion and an excellent yield of 3a (90%) in the second run (Figure SI3). In a third run, conversion decreased to 67% and only traces of the secondary amine 3a were formed together with *N*-benzylideneaniline (5a) as a major product (46%) and aniline (4a) in 16% yield. This is probably due to catalyst poisoning during recycling.

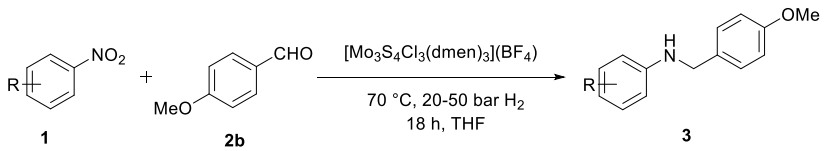
To prove the general applicability of the optimized Mo_3S_4-based catalytic system, the reaction between various functionalized nitro compounds and aldehydes was investigated. More specifically, different nitro compounds were reacted with *p*-anisaldehyde (2b) (Table 2), and as shown in Table 3, the reductive amination of diverse structure aldehydes was carried out with *p*-chloronitrobenzene (1b). To our delight, the corresponding secondary amines were afforded in good to excellent yields. As a general trend, when both the aldehyde and nitroarene are funtionalized with electron-donating groups, such as alkyl, alkoxy or thiomethyl groups, the one-pot reductive amination reaction proceeds smothly towards the formation of the secondary amines. However, the presence of electron-withdrawing groups on the aromatic ring had a high impact on the reductive amination activity since an increased hydrogen pressure (up to 50 bar H_2) is requerid to avoid accumulation of the imine intermediate.

Gratifyingly, both halogen-substituted nitroarenes and aldehydes react to give the corresponding halogenated-amines without any dehalogenation processes affording the corresponding halogenated secondary amines in moderate to excellent yields. Notably, reductive amination of *p*-fluorobenzaldehyde with 1b affords a quantitative yield of the expected alkylated amine (Table 3, entry 5). However, reaction with the *ortho*-isomer requires an increased hydrogen pressure (50 bar H_2) to get a moderate yield of the corresponding secondary amine (Table 3, entry 6). Hence, it seems that reactivity could be affected by both electronic and steric effects.

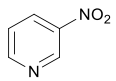
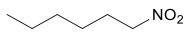
From a synthetic point of view, substrates bearing reducible functionalities are highly attractive. In this respect, we tested some substrates functionalized with nitriles, esters or olefines. To our delight, this moieties were well tolerated, thus furnishing the expected amines in 70-85% isolated yields with the imine being the only byproduct (Table 2, entries 7 and 8; Table 3, entry 8). In addition, a nitro-substituted

heteroarene was tested and the corresponding N-heterocyclic amine was isolated in 81% yield (Table 2, entry 9).

Table 2. Hydrogenation of different nitroarenes with p-anisaldehyde.

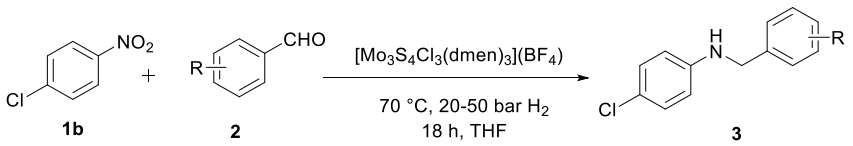


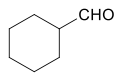
1 2b 3

Entry[a]	Substrate	P (bar)	Conv. [%][b]	Yield amine **3** [%][b]
1	R = H	20	>99	(98)
2[c]	R = 3-Me	20	>99	91
3[d]	R = 3-CF_3	50	>99	(97)
4	R = 4-F	20	>99	>99
5[d]	R = 4-Cl	20	>99	(91)
6	R = 4-I	20	>99	(90)
7[e]	R = 4-CN	50	>99	(70)
8[e]	R = 4-COOMe	50	>99	(83)
9[d, f]		50	>99	(81)
10[c, d, g]		50	>99	61

[a] Reaction conditions: **1** (0.25 mmol), **2b** (0.3 mmol), catalyst (6 mol % related to nitroarene), solvent (2 mL). [b] Determined by GC analysis using hexadecane as an internal standard; yields of isolated products given in parentheses. [c] Traces of aniline as byproduct. [d] Traces of imine as byproduct. [e] Imine as byproduct. [f] 100 ºC of temperature. [g] 150 ºC of temperature; Yield based on ^{1}H NMR using 2,4,6-trimethylphenol as internal standard.

Table 3. Hydrogenation of diverse aldehydes with 1-chloro-4-nitrobenzene



Entry[a]	Substrate	P (bar)	Conv. [%][b]	Yield amine **3** [%][b]
1	R = H	40	>99	(95)
2[c]	R = *i*Pr	20	>99	(83)
3	R = 3-OMe; 4-OEt	20	>99	(97)
4	R = 4-SMe	20	>99	(95)
5	R = 4-F	20	>99	>99
6[c]	R = 2-F	50	>99	(67)
7[c]	R = 4-Br	40	>99	(76)
8[c]	R = 3-$CHCH_2$	40	>99	(85)
9[d]		40	>99	60 (50)

[a] Reaction conditions: **1b** (0.25 mmol), **2** (0.3 mmol), catalyst (6 mol % related to nitroarene), solvent (2 mL). [b] Determined by GC analysis using hexadecane as an internal standard; yields of isolated products given in parentheses. [c] Imine as byproduct. [d] Aniline and traces of imine as byproducts.

Nowadays, the reductive amination of aldehydes with aliphatic nitrocompounds remains as an important challenge. Interestingly, in the presence of our Mo_3S_4-based catalyst reaction between 2b and 1-nitrohexane leads to the formation of the secondary amine in 61% yield (Table 2, entry 10). Moreover, our catalytic system also works with cyclic aliphatic aldehydes. Reductive amination of cyclohexanecarboxaldehyde with 1b affords a moderate yield (60%) of the desired amine (Table 3, entry 9).

Conclusions

In conclusion, we have developed an atom-efficient catalytic protocol for the synthesis of secondary amines through a one-pot reductive amination reaction from easily available nitroarenes and aldehydes using hydrogen as reducing agent. The use of a well-defined diamino molecular Mo_3S_4 clusters as catalyst allows for successful reductive amination of aldehydes with the in situ generated primary amines selectively affording a variety of secondary amines in good to excellent yields. Remarkably, this procedure applies for aromatic as well as for aliphatic nitro compounds or aldehydes. Spectrometric and spectroscopic techniques show no changes in cluster composition or evidences of cluster fragmentation during the catalytic reaction. Mechanistic investigations on the catalytic process which combine theory with experiment are in progress.

Experimental Section

Synthesis of the catalyst: The catalyst $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ was prepared starting from the $[Mo_3S_4(tu)_8(H_2O)]Cl_4{\cdot}4H_2O$ thiourea precursor according to the literature.[6]

General procedure for the one-pot reductive amination: A 8 mL glass vial containing a stirring bar was sequentially charged with the molybdenum catalyst (4.4 mg, 0.005 mmol of $[Mo_3S_4Cl_3(dmen)_3](BF_4)$), nitrobenzene (10 μL, 0.097 mmol), benzaldehyde (12 μL, 0.12 mmol), *n*-hexadecane (15 μL; added as an internal standard) and 2 mL of THF. Afterwards, the reaction vial was capped with a septum equipped with a needle and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to 20 bar and placed into an aluminum block, which was

preheated at 70 °C. After 18 h, the autoclave was cooled to room temperature and the hydrogen was released. Ethyl acetate (2 mL) was then added, and a sample was taken to be analyzed by GC. To determine the isolated yields of the anilines, the general procedure was scaled up by the factor of 2.5, and no internal standard was added. After completion of the reaction, the mixture was purified by silica column chromatography (n-heptane/ethyl acetate mixtures) to give the corresponding anilines. In the case of the nitroalkane, 2,4,6-trimehtylphenol was added as internal standard and the yield was calculated based on ^{1}H NMR.

Acknowledgements

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SUPPORTING INFORMATION

Selective reductive amination of aldehydes with from nitro compounds catalyzed by molybdenum sulfide clusters

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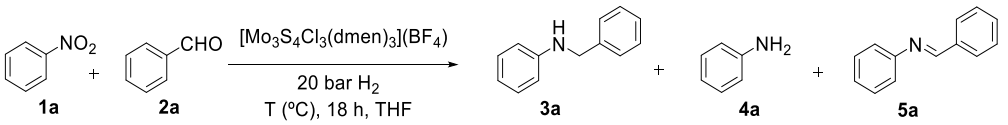
1. Materials and Methods.

Nitro compounds, aldehydes and internal standards were obtained from commercial sources and used as received. Organic solvents were dried by standard methods before use. The ^{1}H-NMR and ^{13}C-NMR spectra of the isolated anilines were recorded on a Bruker AV 300 or Bruker AV 400 spectrometer. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) in Hz. For ^{1}H-NMR all chemical shifts are reported relative to tetramethylsilane (δ 0.0 ppm in $CDCl_3$) or d-solvent peaks (δ 77.16 ppm $CDCl_3$) for ^{13}C-NMR. All measurements were carried out at room temperature unless otherwise stated. The GC yields were determined by GC-FID using *n*-hexadecane as an internal standard. Gas chromatography analyses were performed on an Agilent 7820A GC System equipped with a FID and a capillary column Agilent (HP-5, 30m x 0.32 mm x 0.25 μm). Mass determination was carried out on a GC-Mass Agilent 5973 Network equipped with a mass selective detector. Electrospray mass spectrum of the catalyst after the catalytic reaction was recorded with a Quattro LC (quadrupole-hexapole-quadrupole) mass spectrometer with an orthogonal Z-spray electrospray interface (Micromass, Manchester, UK). The cone voltage was set at 20 V using CH_3CN as the mobile phase solvent. Sample solutions have been infused via syringe pump directly connected to the ESI source at a flow rate of 10 μL/min and a capillary voltage of 3.5 kV was used in the positive scan mode. Nitrogen was employed as drying and nebulizing gas. Isotope experimental patterns were compared with theoretical patterns obtained using the MassLynx 4.1 program.[2] ^{1}H spectrum of the reaction mixture was recorded on a Bruker Avance III HD 300 MHz using CD_3CN as solvent.

2. Advanced experimental details for the optimization of the reaction conditions.

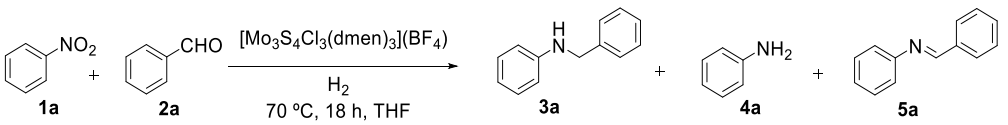
Table SI1. Influence of the temperature.[a]



Entry	Temperature [ºC]	Conversion [%][b]	Yield **3a** [%][b]	Yield **4a** [%][b]	Yield **5a** [%][b]
1	100	>99	99	1	0
2	70	>99	99	0	0
3	60	>99	42	17	38

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), H_2 (20 bar), catalyst (5 mol%), THF (2 mL), 18 h. [b] Determined by GC analysis using *n*-hexadecane as an internal standard.

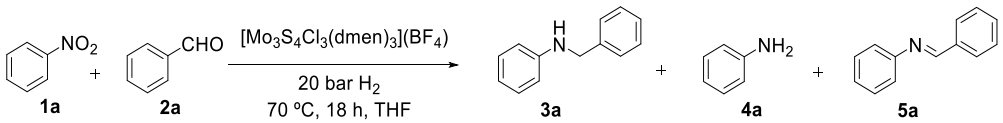
Table SI2. Variation of the pressure of H_2.[a]



Entry	Pressure [bar]	Conversion [%][b]	Yield **3a** [%][b]	Yield **4a** [%][b]	Yield **5a** [%][b]
1	20	>99	99	0	0
2	15	>99	65	16	17

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (5 mol%), THF (2 mL), 18 h, 70ºC. [b] Determined by GC analysis using *n*-hexadecane as an internal standard.

Table SI3. Catalyst loading variation.[a]



Entry	Catalyst loading [mol%]	Conversion [%][b]	Yield **3a** [%][b]	Yield **4a** [%][b]	Yield **5a** [%][b]
1	0	0	0	0	0
2	1	73	0	20	51
3	2	>99	48	18	30
4	3	>99	92	2	5
5	4	>99	95	0	3
6	5	>99	99	0	0
7[c]	5	48	0	7	38

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), H_2 (20 bar), THF (2 mL), 18 h, 70 ºC. [b] Determined by GC analysis using *n*-hexadecane as an internal standard. [c] Reaction time: 4 h.

3. Characterization of the catalyst after the catalytic reaction.

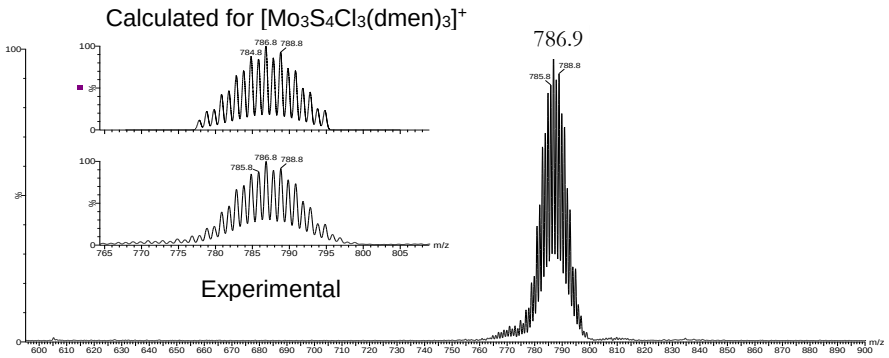


Figure SI1. ESI mass spectrum of the catalyst in CH_3CN at 20 V after the catalytic reaction between **1a** and **2a**.

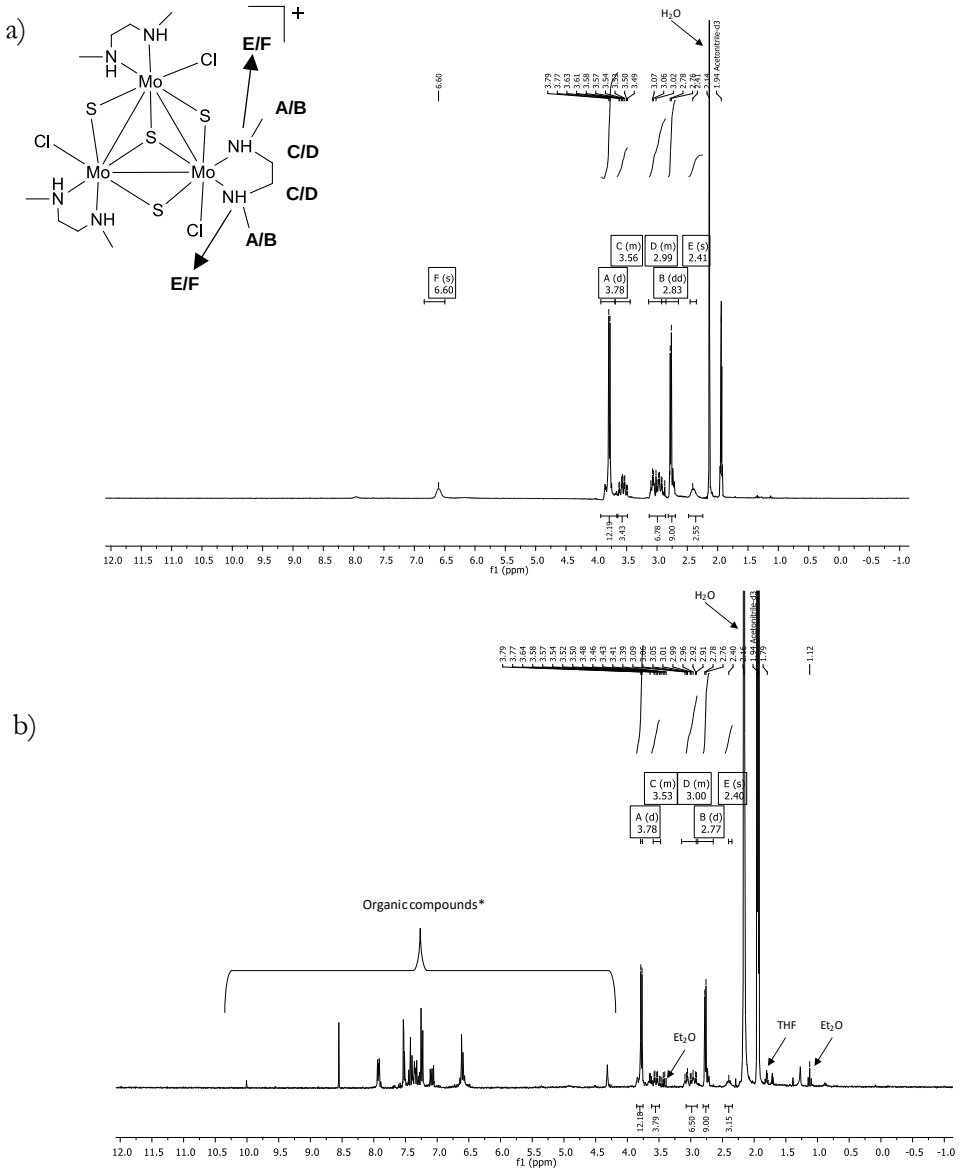
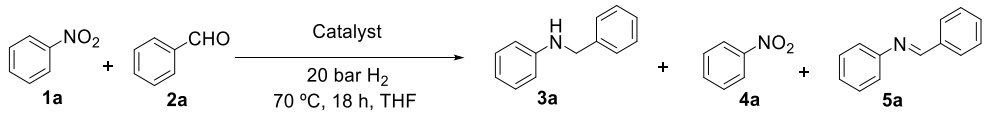


Figure SI2. (a) ^{1}H NMR spectrum of the $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ cluster in CD_3CN; (b) ^{1}H NMR spectrum of the reaction mixture after the catalytic process. For this last experiment, the mixture was taken to dryness, washed with diethyl ether, dried and redissolved in CD_3CN. *Organic compounds: *N*-benzylaniline (**3a**), benzaldehyde (**2a**) and aniline (**4a**).

4. Catalyst recycling experiments for the reductive amination between nitrobenzene and benzaldehyde.



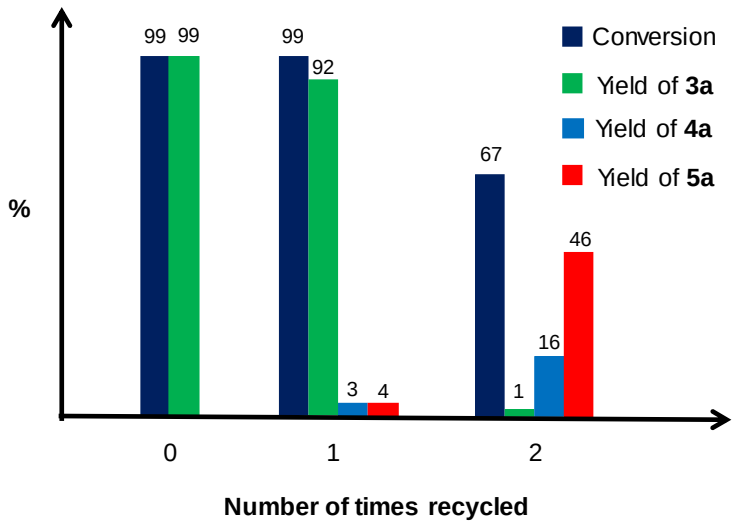
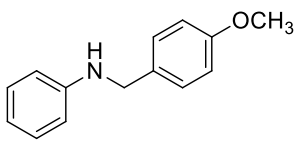


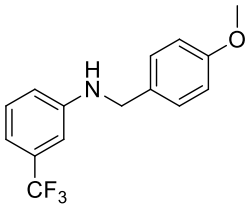
Figure SI3. Recycling of the catalyst for the reductive amination reaction.
Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst, H_2 (20 bar), THF (2 mL), 18 h, 70 ºC. Conversions and yields were determined by GC using *n*-hexadecane as standard (15 μL).

5. Characterization data of isolated products.

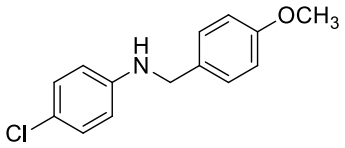


N-(4'-Methoxybenzyl)aniline[3]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 7.21 – 7.11 (m, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.64 – 6.58 (m, 1H), 4.22 (s, 2H), 3.92 (br s, 1H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

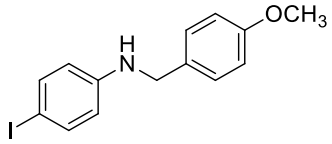
δ 158.96, 148.32, 131.53, 129.35, 128.90, 117.59, 114.13, 112.94, 55.39, 47.89; MS (EI): *m/z* (rel. Int) 213.



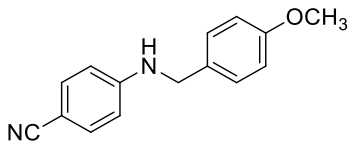
N-(4-methoxybenzyl)-3-(trifluoromethyl)aniline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 3H), 6.90 – 6.72 (m, 4H), 6.67 – 6.61 (m, 1H), 4.16 (s, 2H), 4.04 (br s, 1H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.18, 148.39, [132.28, 131.86, 131.44, 131.02 (q, $^{2}J_{C\text{-}F}$ = 32 Hz)], 130.67, [129.90, 126.29, 122.68, 119.14 (q, $^{1}J_{C\text{-}F}$ = 272 Hz)], 129.75, 128.96, 115.84, 114.27, [114.02, 113.97, 113.92, 113.87 (q, $^{3}J_{C\text{-}F}$ = 4 Hz)], [109.21, 109.16, 109.11, 109.06 (q, $^{3}J_{C\text{-}F}$ = 4 Hz)], 55.40, 47.71; MS (EI): *m/z* (rel. int.) 281.



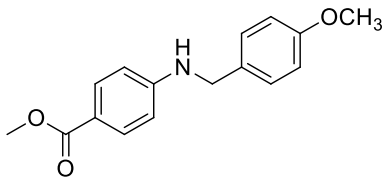
N-(4'-Methoxybenzyl)-4-Chloroaniline: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.45 (d, *J* = 8.8 Hz, 2H), 4.13 (s, 2H), 3.93 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.06, 146.82, 131.01, 129.16, 128.84, 122.12, 114.20, 114.02, 55.42, 47.95; MS (EI): *m/z* (rel. int.) 247.



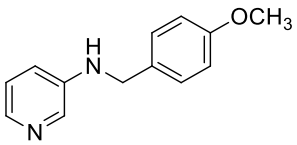
N-(4'-Methoxybenzyl)-4-Iodoaniline[3]: Isolated yield: X %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 8.8 Hz, 2H), 4.22 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.10, 147.81, 137.91, 130.91, 128.84, 115.20, 114.23, 78.17, 55.45, 47.70; MS (EI): *m/z* (rel. int.) 339.



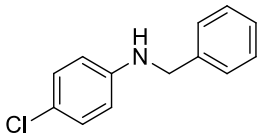
4-(4-Methoxybenzylamino) benzonitrile: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 2H), 7.24 – 7.12 (m, 2H), 6.86 – 6.76 (m, 2H), 6.55 – 6.45 (m, 2H), 4.49 (s, 1H), 4.21 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.27, 151.22, 133.80, 129.84, 128.79, 120.53, 114.35, 112.47, 99.02, 55.42, 47.09; MS (EI): *m/z* (rel. int.) 238.



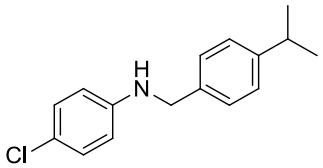
Methyl 4-((4-methoxybenzyl)amino)benzoate[4]**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.38 (br s, 1H), 4.21 (s, 2H), 3.75 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.40, 159.15, 151.90, 131.64, 130.43, 128.85, 118.61, 114.25, 111.70, 55.40, 51.61, 47.23; MS (EI): *m/z* (rel. int.) 271.



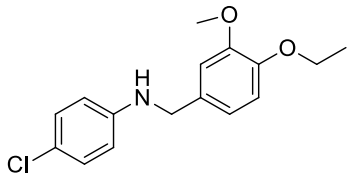
N-(4-methoxybenzyl)pyridin-3-amine[5]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 2 Hz, 1H), 7.95 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.06 (dd, *J* = 8.0 Hz, 4.7 Hz, 1H), 6.91 – 6.85 (m, 3H), 4.26 (s, 2H), 4.04 (br s, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.13, 144.18, 138.90, 136.21, 130.57, 128.86, 123.83, 118.69, 114.25, 55.42, 47.46; MS (EI): *m/z* (rel. int.) 214.



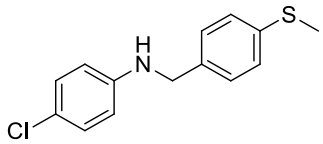
N-benzyl-4-chloroaniline[6]**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 4H), 7.33 – 7.29 (m, 1H), 7.17 – 7.09 (m, 2H), 6.60 – 6.52 (m, 2H), 4.32 (s, 2H), 4.08 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.77, 139.06, 129.18, 128.82, 127.53, 127.48, 122.20, 114.03, 48.45; MS (EI): *m/z* (rel. int.) 217.



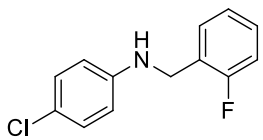
4-chloro-N-(4-isopropylbenzyl)aniline[7]**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.07 (m, 4H), 7.07 – 6.95 (m, 2H), 6.50 – 6.39 (m, 2H), 4.15 (s, 2H), 3.90 (br s, 1H), 3.05 – 2.45 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.23, 146.88, 136.36, 129.16, 127.64, 126.86, 122.08, 113.98, 48.23, 33.92, 24.14; MS (EI): *m/z* (rel. int.) 259.



4-chloro-N-(4-ethoxy-3-methoxybenzyl)aniline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 – 6.92 (m, 2H), 6.86 – 6.67 (m, 3H), 6.54 – 6.36 (m, 2H), 4.11 (s, 2H), 4.05 – 3.94 (m, 2H), 3.82 (s, 1H), 3.75 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.55, 147.68, 146.84, 131.44, 129.08, 122.07, 119.70, 113.99, 112.81, 111.06, 64.44, 55.97, 48.32, 14.89; MS (EI): m/z (rel. int.) 291.

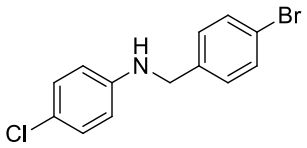


4-chloro-N-(4-(methylthio)benzyl)aniline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.09 (m, 4H), 7.10 – 6.89 (m, 2H), 6.61 – 6.35 (m, 2H), 4.18 (s, 2H), 3.96 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.68, 137.56, 135.99, 129.21, 128.07, 127.14, 122.29, 114.08, 48.03, 16.13; MS (EI): m/z (rel. int.) 263.

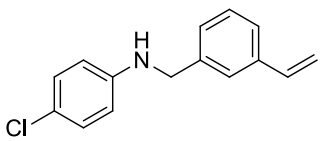


4-chloro-N-(2-fluorobenzyl)aniline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 1H), 7.22 – 7.12 (m, 1H), 7.06 – 6.99 (m, 3H), 6.99 – 6.93 (m, 1H), 6.52 – 6.44 (m, 2H), 4.29 (s, 2H), 4.00 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [162.64, 159.38 (d, $^{1}J_{C\text{-}F}$ = 246.0 Hz)], 146.43, [129.48, 129.42 (d, $^{3}J_{C\text{-}F}$ = 4.4 Hz)], 129.21, [129.16, 129.06 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz)], [126.06, 125.86 (d, $^{2}J_{C\text{-}F}$ = 14.4 Hz)], [124.39, 124.34 (d, $^{4}J_{C\text{-}F}$ =

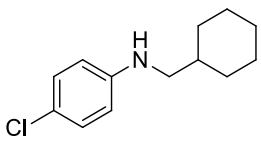
3.5 Hz)], 122.44, [115.69, 115.41 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz)], 114.33, [42.10, 42.04 (d, $^{3}J_{C\text{-}F}$ = 4.3 Hz)]; MS (EI): *m/z* (rel. int.) 235.



N-(4-bromobenzyl)-4-chloroaniline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 4.27 (s, 2H), 4.10 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 146.42, 138.14, 131.89, 129.22, 129.08, 122.49, 121.19, 114.09, 77.16, 47.79; MS (EI): *m/z* (rel. int.) 296.



4-chloro-N-(3-vinylbenzyl)aniline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (qd, *J* = 7.5, 3.7 Hz, 4H), 7.02 – 6.94 (m, 2H), 6.58 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.48 – 6.37 (m, 2H), 5.63 (d, *J* = 18.4 Hz, 1H), 5.14 (d, *J* = 10.9 Hz, 1H), 4.16 (s, 2H), 3.93 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.66, 139.26, 138.04, 136.64, 129.12, 128.95, 126.91,125.30, 122.18, 114.31, 113.96, 48.35; MS (EI): *m/z* (rel. int.) 243.



4-chloro-N-(cyclohexylmethyl)aniline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 – 7.07 (m, 2H), 6.54 – 6.47 (m, 2H), 3.68 (br s, 1H), 2.92 (d, *J* = 6.7 Hz, 2H), 1.83 – 1.70

(m, 4H), 1.62 – 1.49 (m, 1H), 1.34 – 1.12 (m, 4H), 1.04 – 0.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.31, 129.12, 121.45, 113.76, 50.81, 37.61, 31.38, 26.66, 26.07; MS (EI): *m/z* (rel. int.) 223.

5. References.

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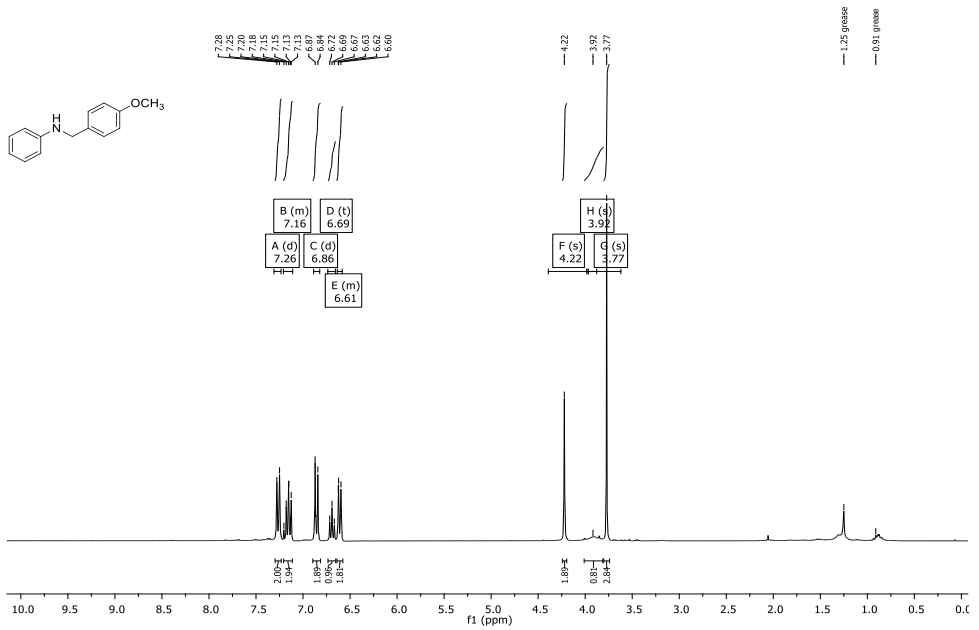
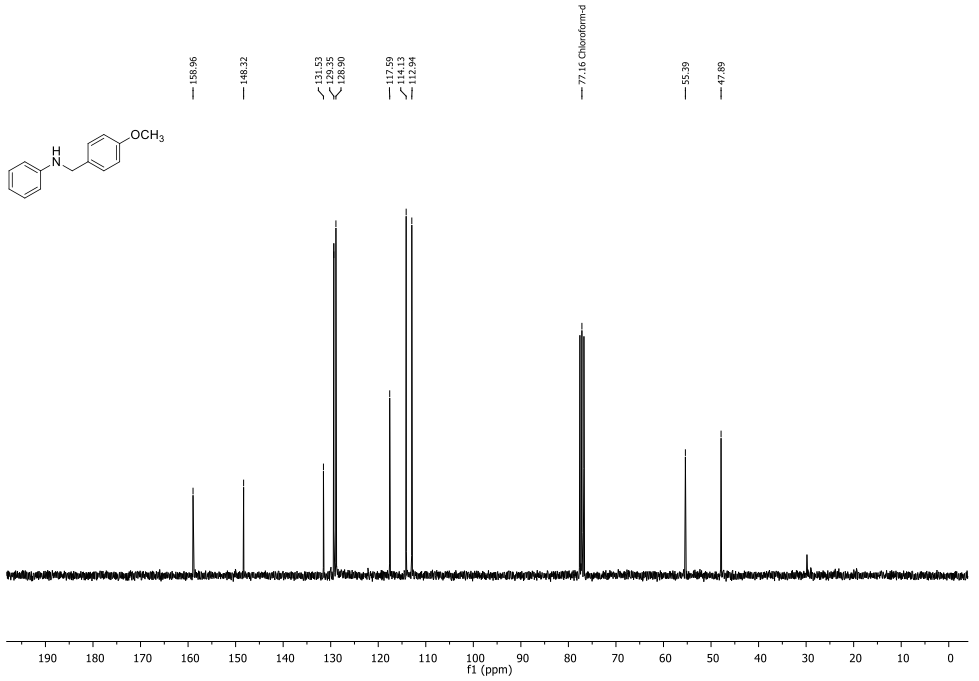
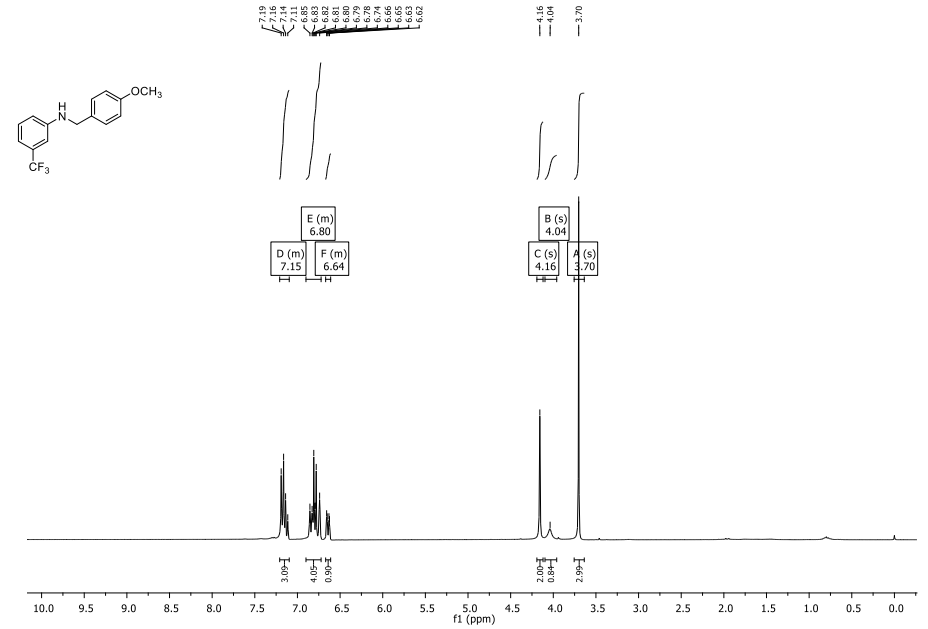
7 Q. Peng, Y. Zhang, F. Shi and Y. Deng, *Chem. Commun.*, **2011**, *47*, 6476.

6. ^{1}H NMR and ^{13}C NMR spectra of isolated products.



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CF3
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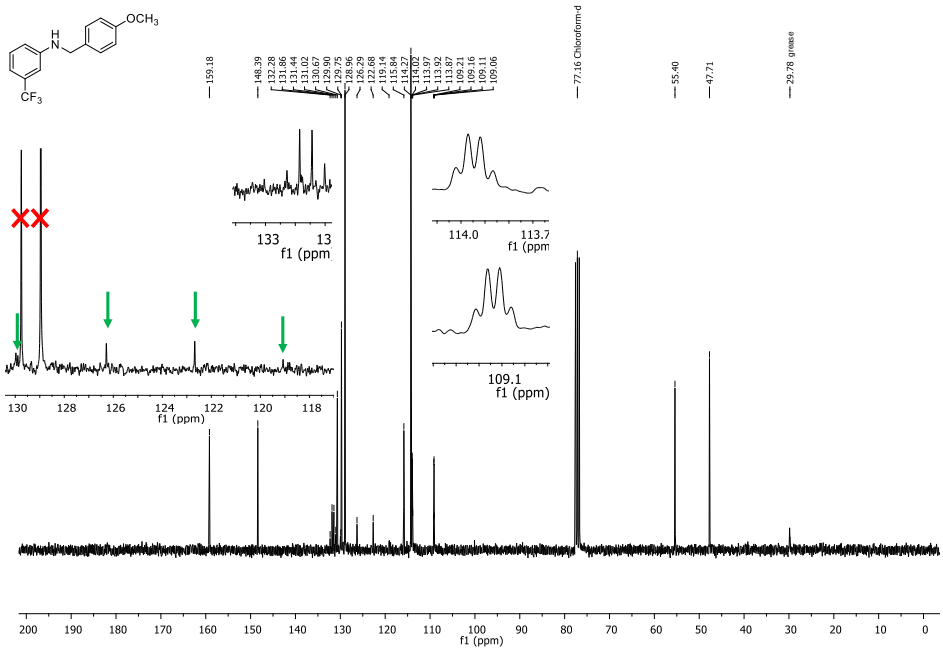
D (m) 7.15
F (m) 6.64
B (s) 4.04
C (s) 4.16
A (s) 3.70
f1 (ppm)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CF3
77.16 Chloroform-d
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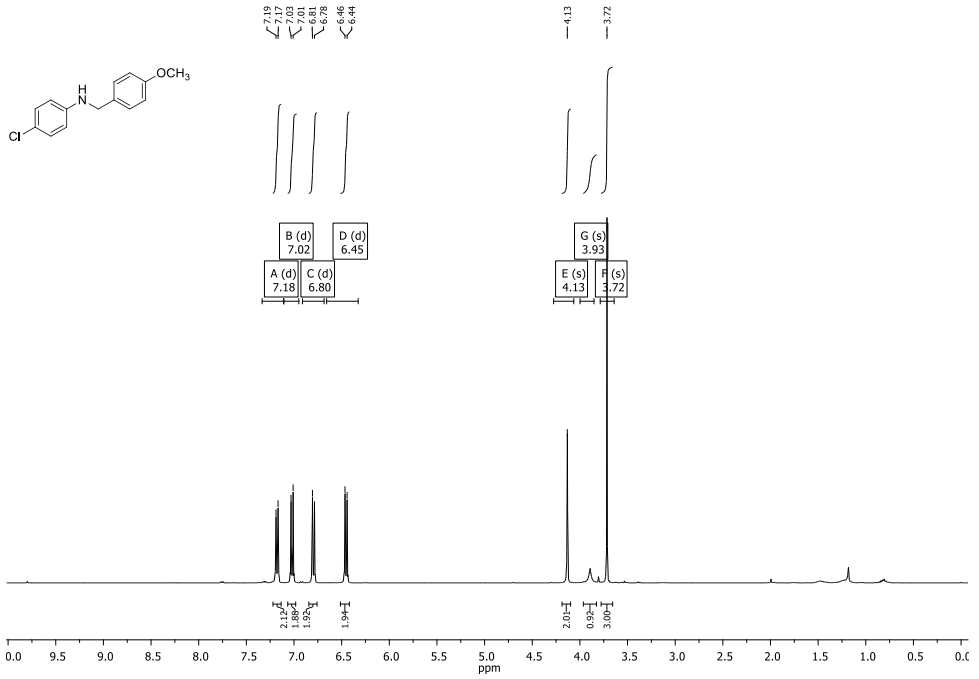
47.71
29.78 grease
133
13
f1 (ppm
114.0
113.7
109.1
f1 (ppm)


7.19
7.17
7.03
7.01
6.81
6.78
6.46
6.44
4.13
3.72
OCH3
H
N
Cl
B (d)
7.02
D (d)
6.45
A (d)
7.18
C (d)
6.80
G (s)
3.93
E (s)
4.13
F (s)
3.72
2.13
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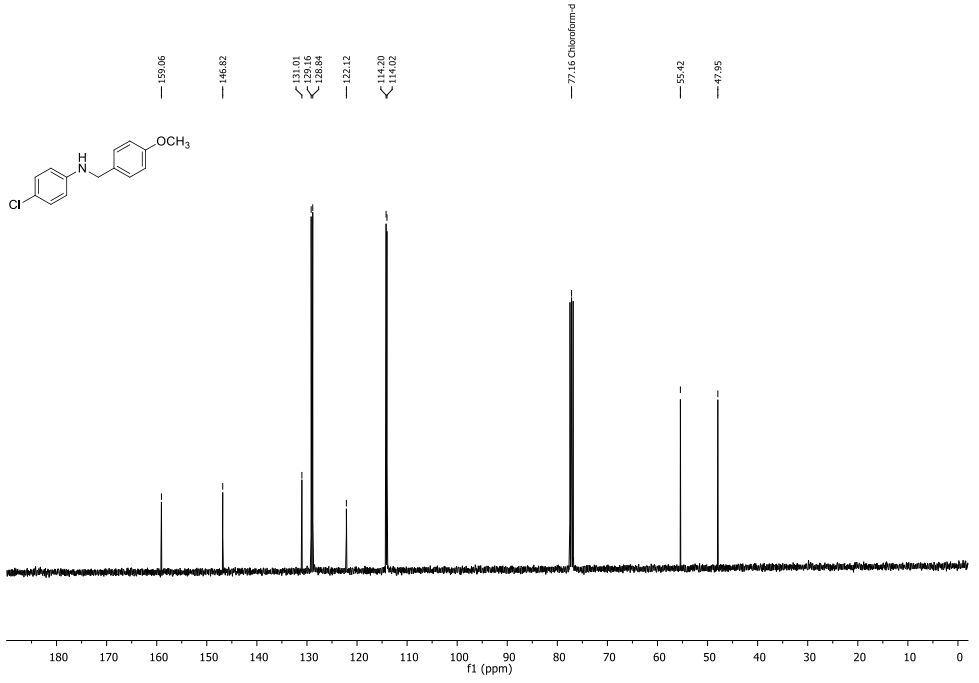
1.92
1.94
2.01
0.92
3.00
ppm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146.82
131.01
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122.12
114.20
114.02
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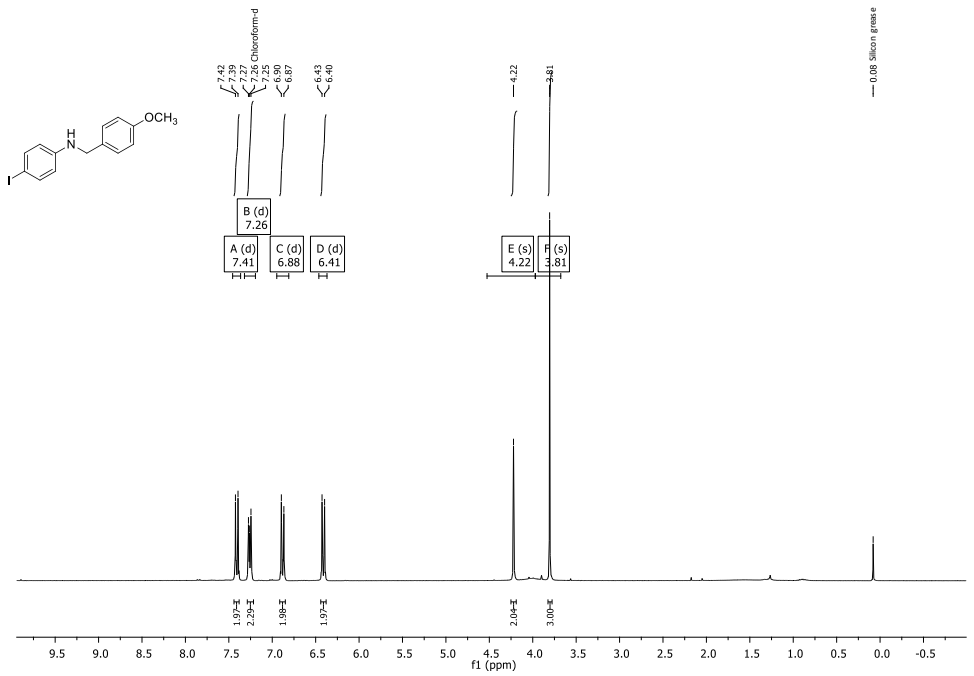
55.42
47.95
OCH3
H
N
Cl
f1 (ppm)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7.39
7.27
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7.22
6.90
6.87
6.43
6.40
4.22
3.81
0.08 Silicon grease
OCH3
H
N
I
B (d)
7.26
A (d)
7.41
C (d)
6.88
D (d)
6.41
E (s)
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F (s)
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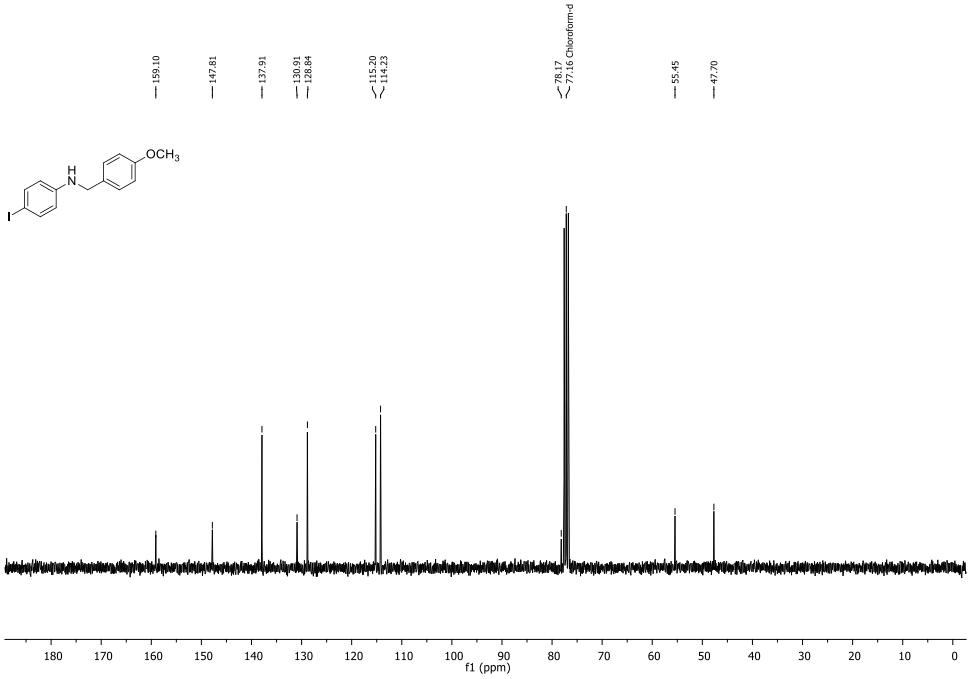
1.98
1.97
2.04
3.00
f1 (ppm)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130.91
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115.20
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78.17
77.16 Chloroform-d
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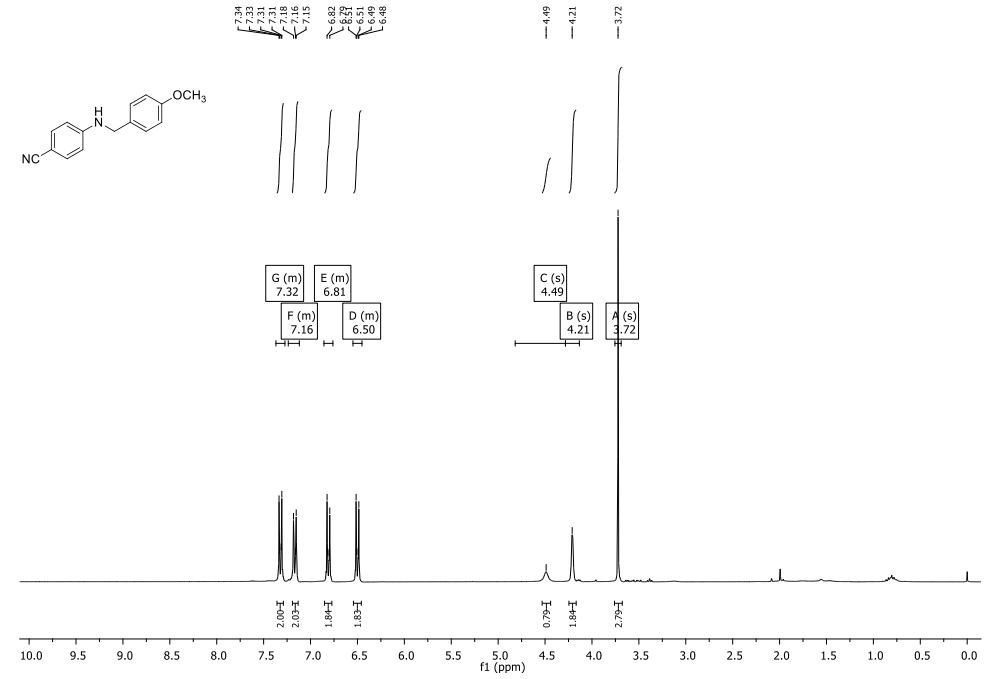
H
N
I
f1 (ppm)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3.72
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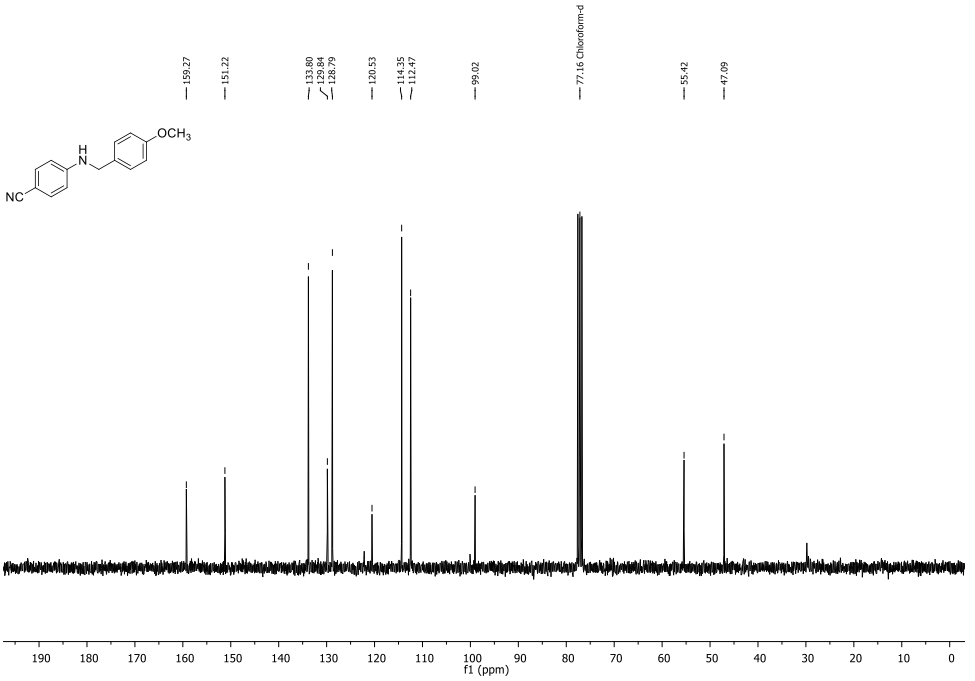
H
N
NC
G (m)
7.32
E (m)
6.81
F (m)
7.16
D (m)
6.50
C (s)
4.49
B (s)
4.21
A (s)
3.72
2.00
2.03
1.84
1.83
0.79
1.84
2.79
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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151.22
133.80
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128.79
120.53
114.55
112.47
99.02
77.16 Chloroform-d
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47.09
OCH3
H
N
NC
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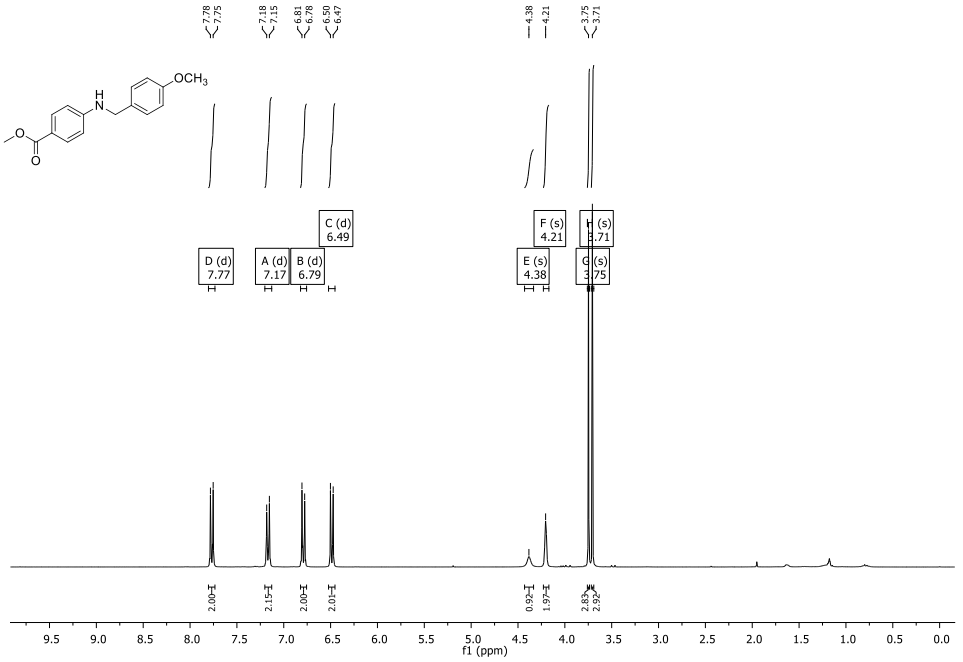
f1 (ppm)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6.78
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4.21
3.75
3.71
OCH3
O
O
D (d)
7.77
A (d)
7.17
B (d)
6.79
C (d)
6.49
E (s)
4.38
F (s)
4.21
G (s)
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H (s)
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2.00
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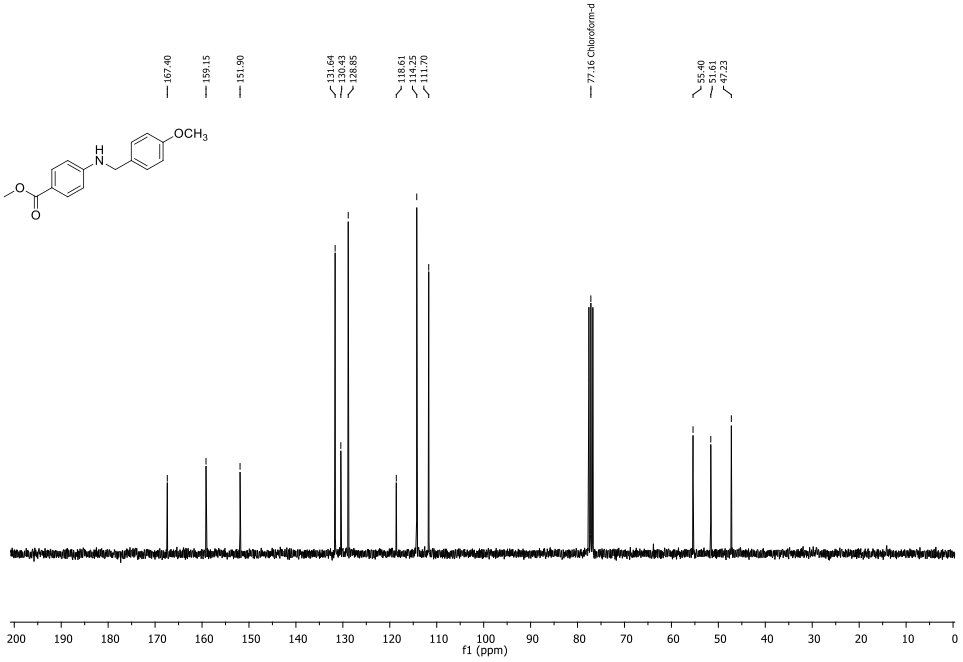
2.92
f1 (ppm)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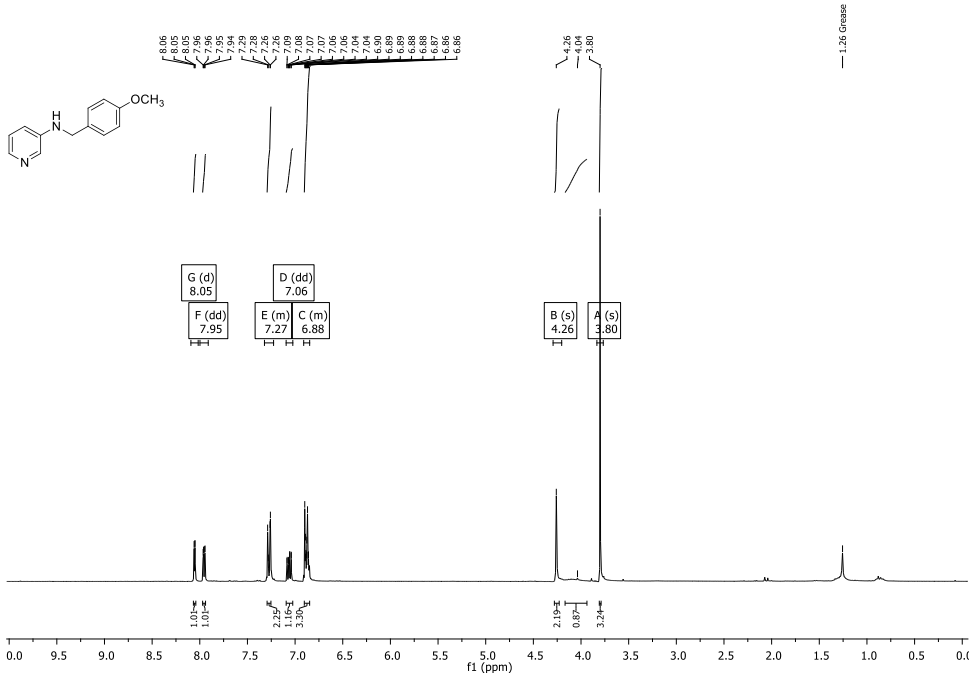
47.23
OCH3
O
O
f1 (ppm)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8.05
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H
N
N
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F (dd)
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D (dd)
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E (m)
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C (m)
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B (s)
4.26
A (s)
3.80
1.01
1.01
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1.16
3.35
2.19
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3.24
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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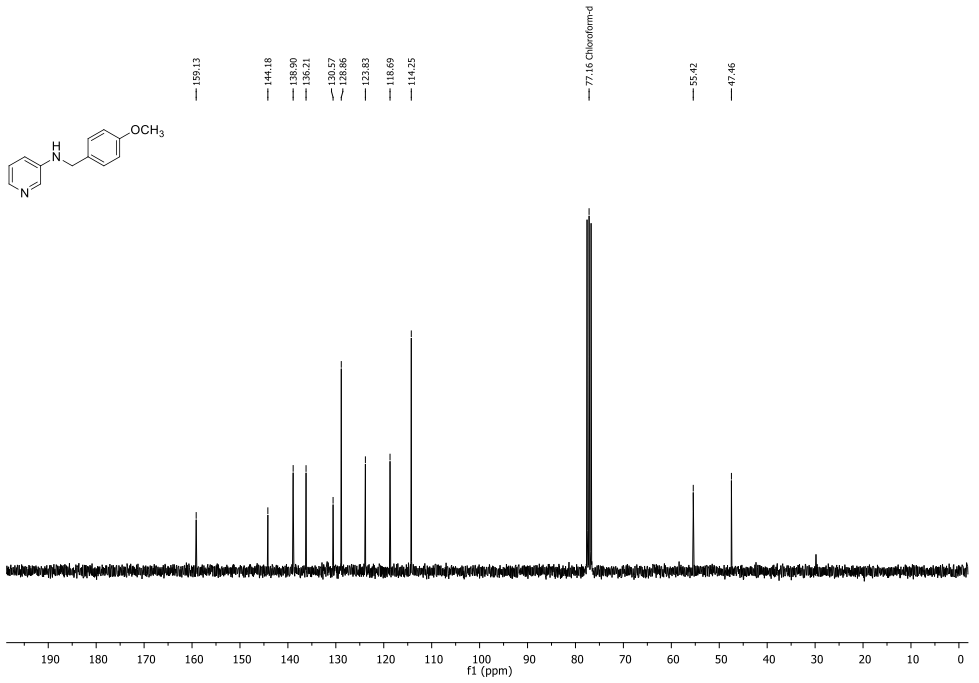
1.0
0.5
f1 (ppm)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136.21
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128.86
123.83
118.69
114.25
77.16 Chloroform-d
55.42
47.46
OCH3
H
N
N
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
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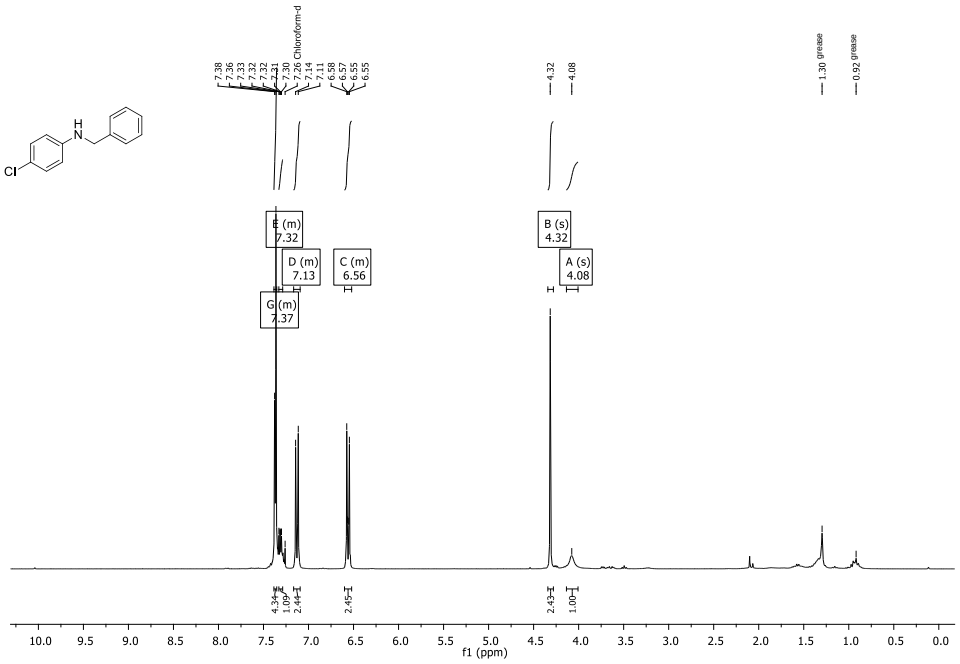
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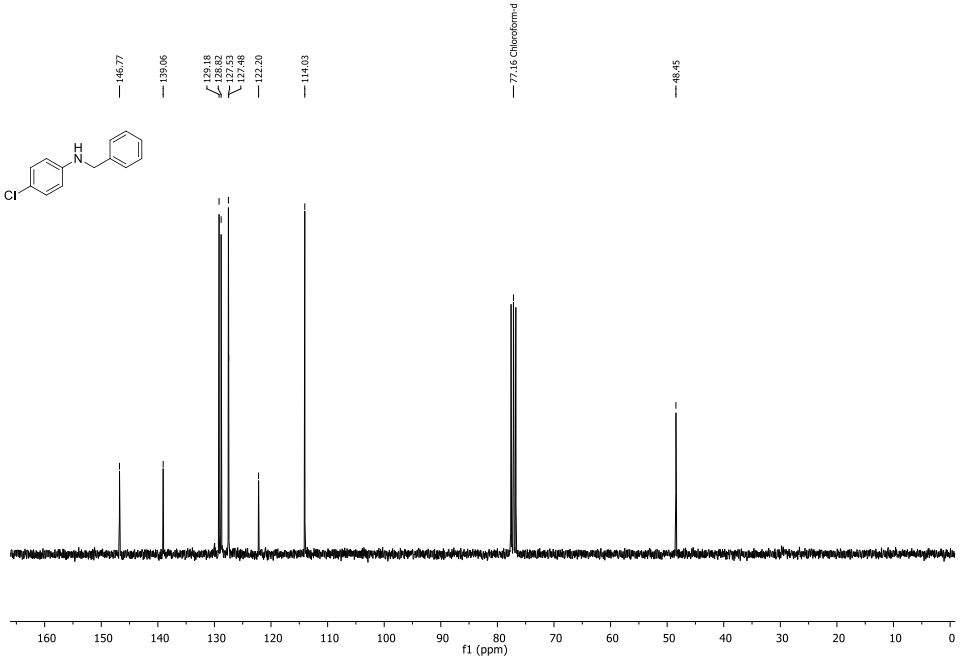
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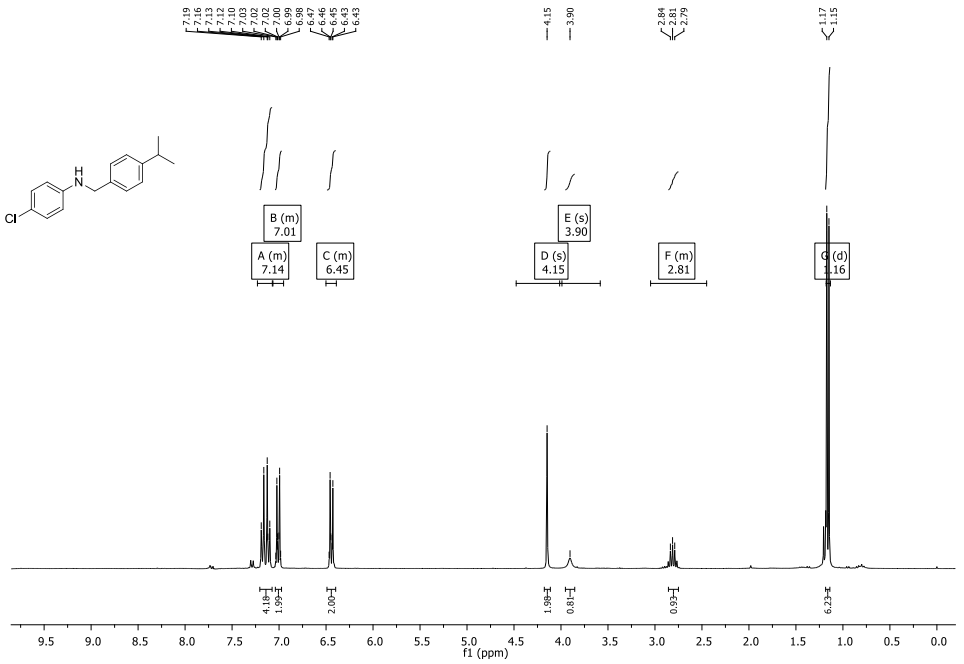
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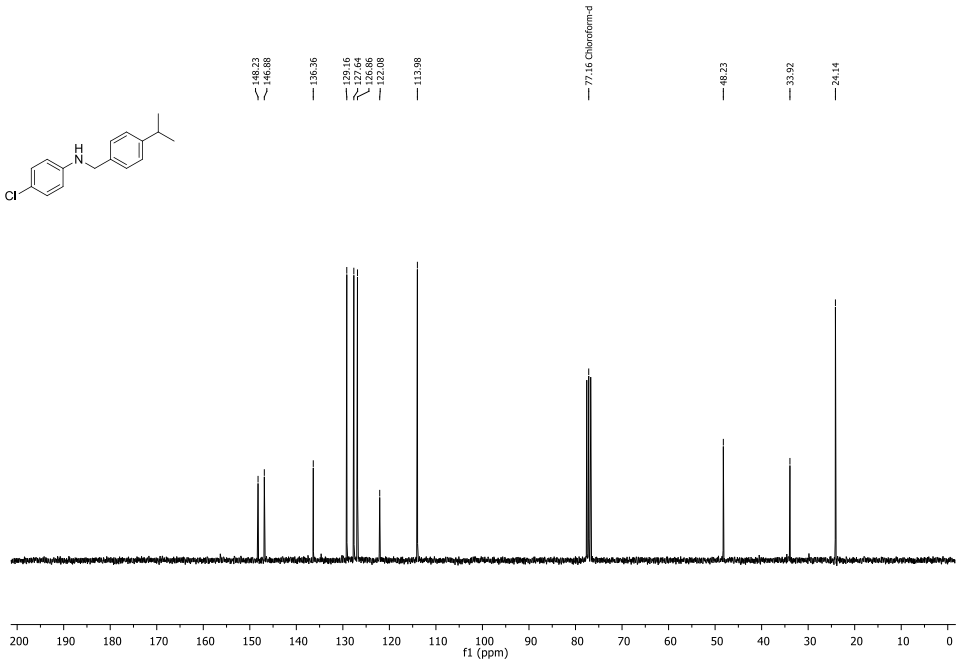
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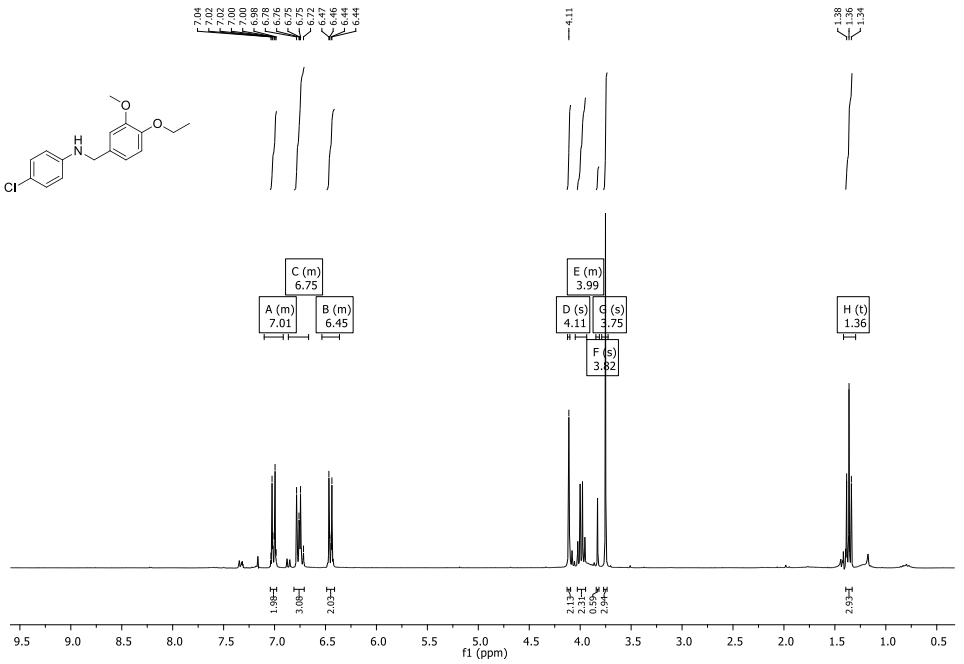
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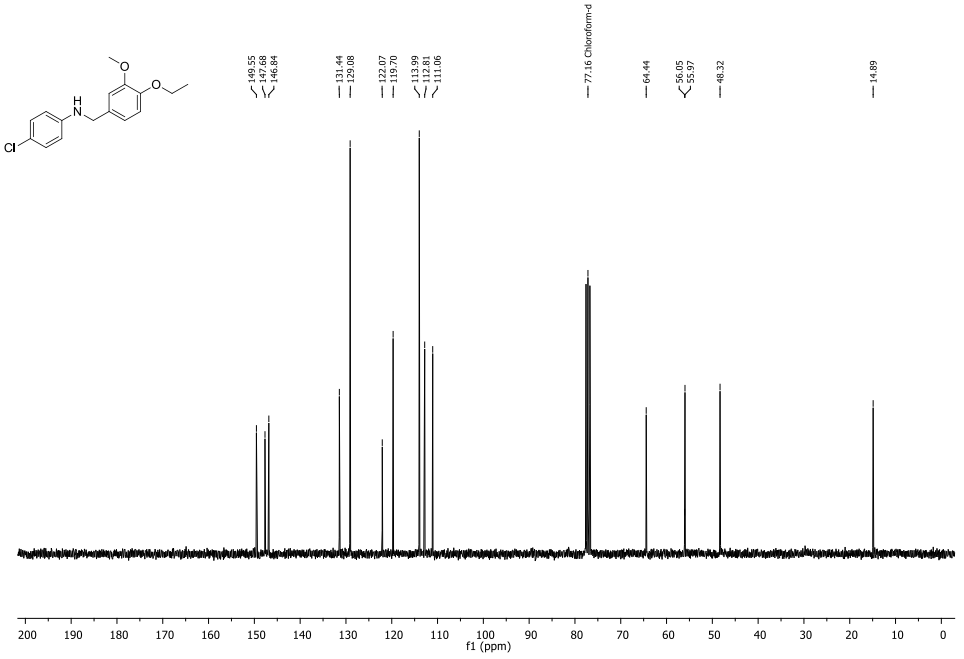
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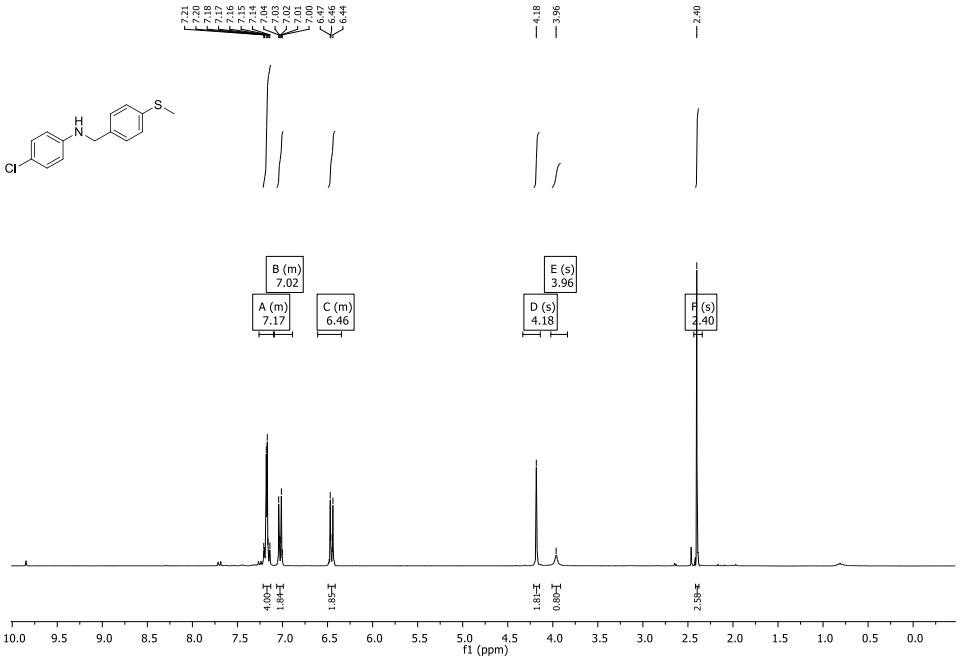
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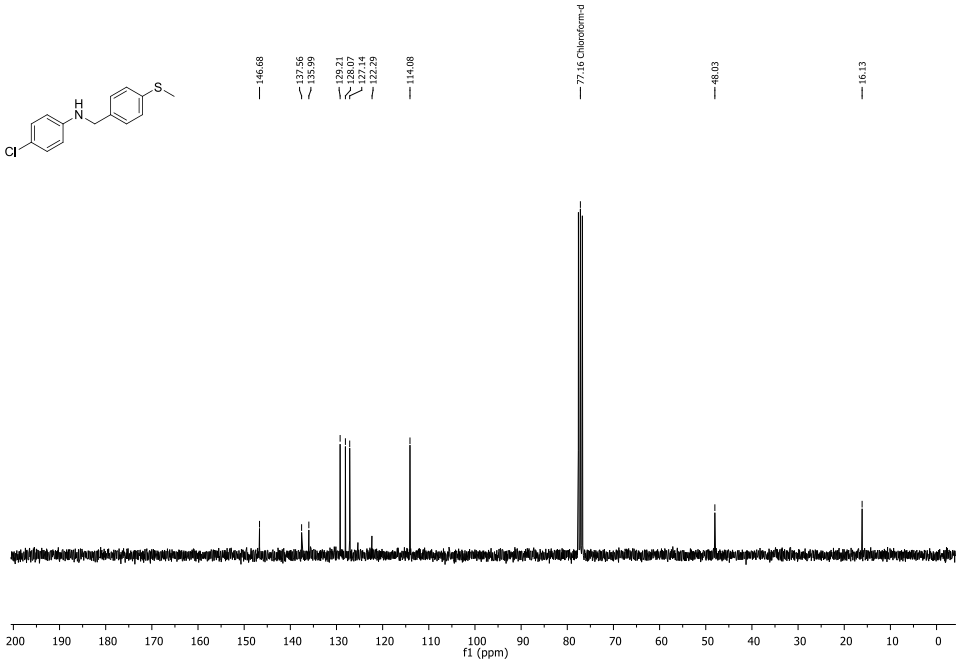
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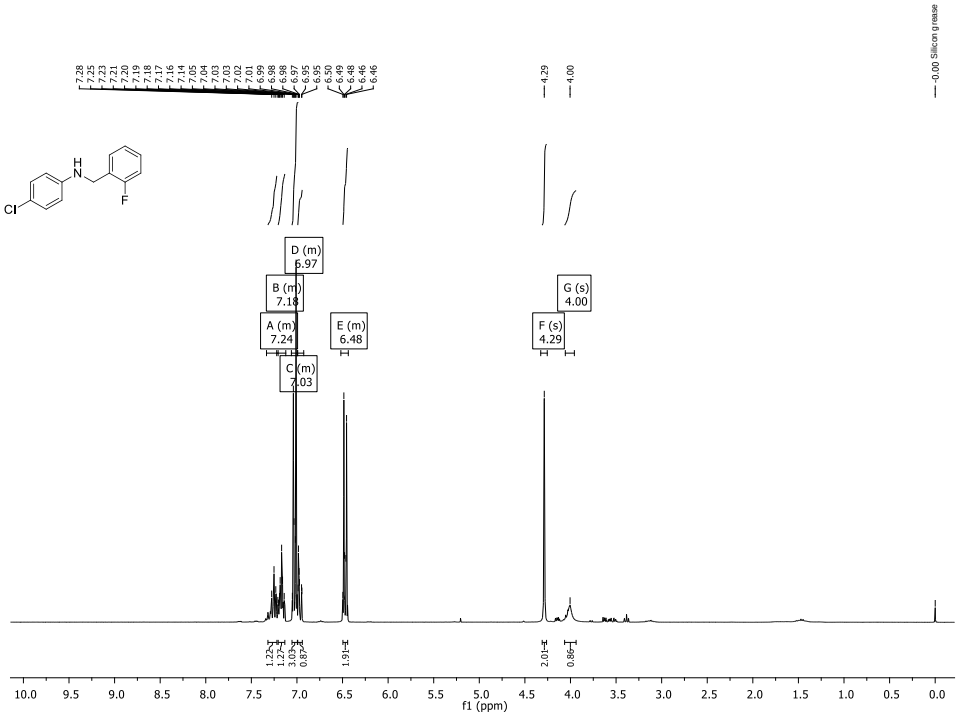
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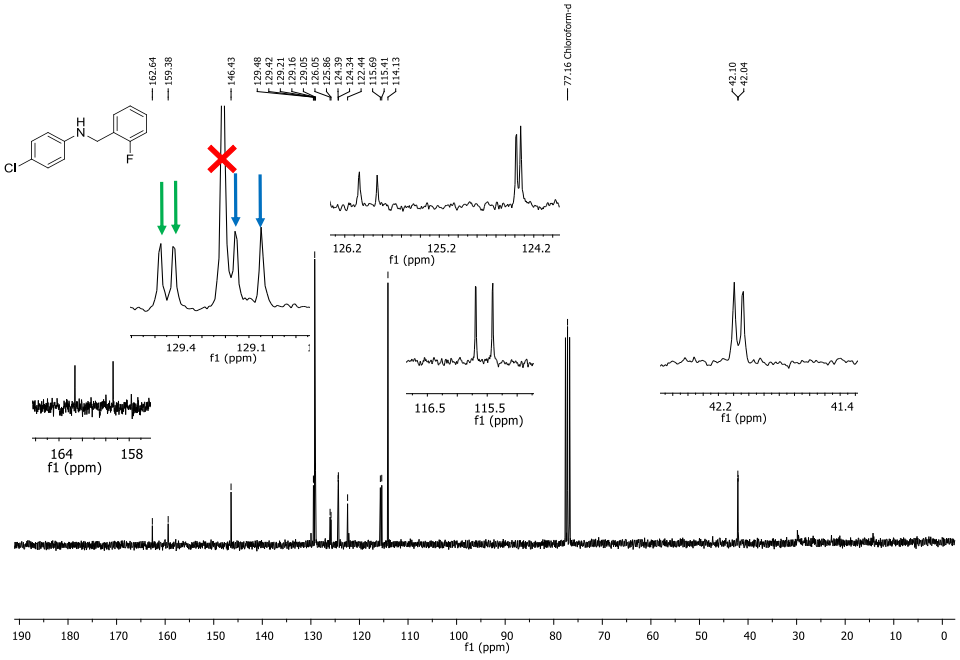
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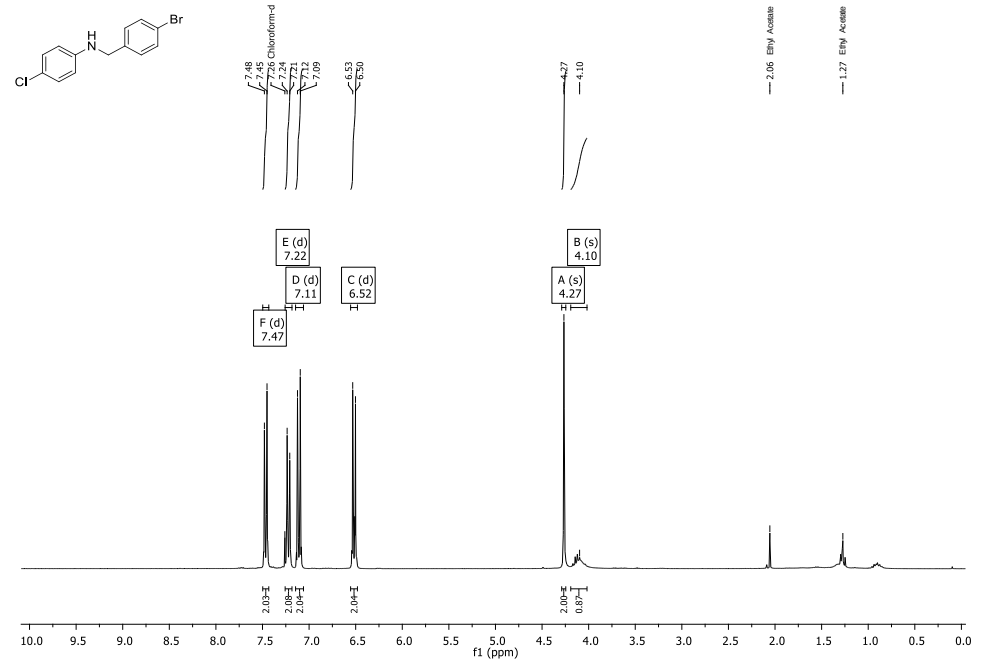
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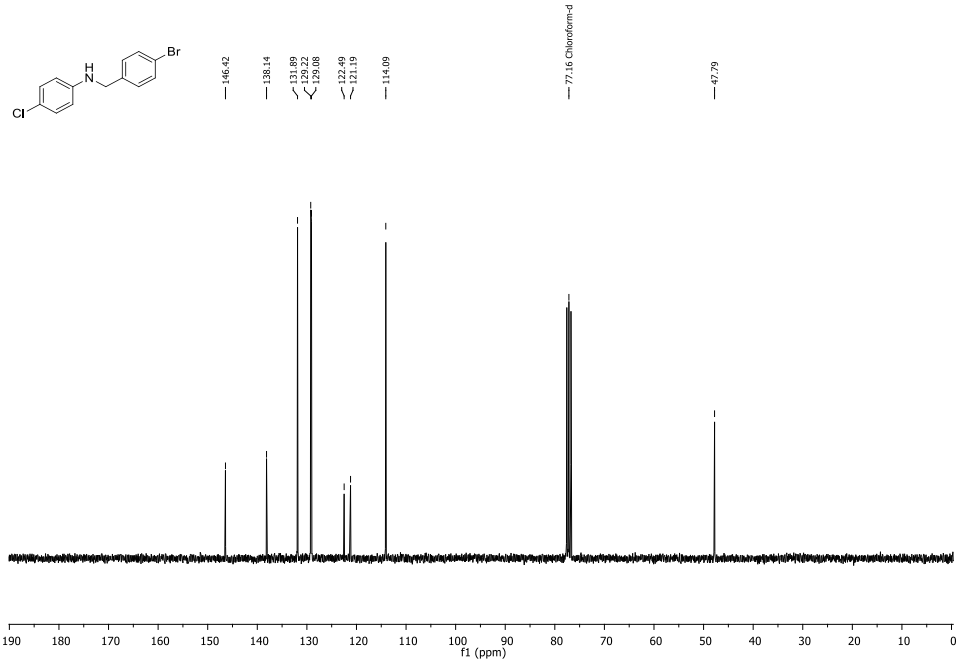
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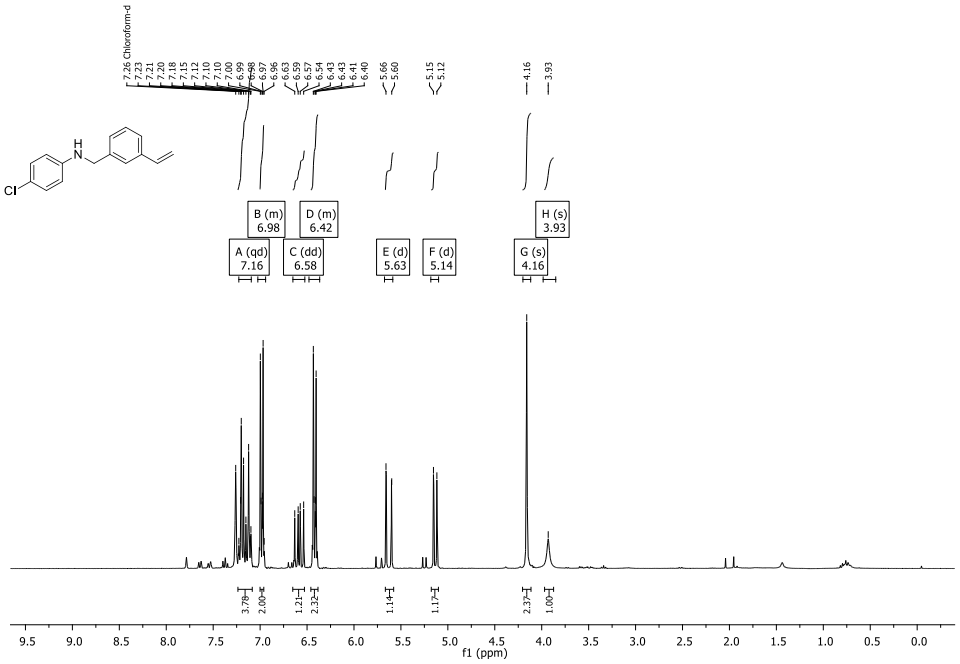
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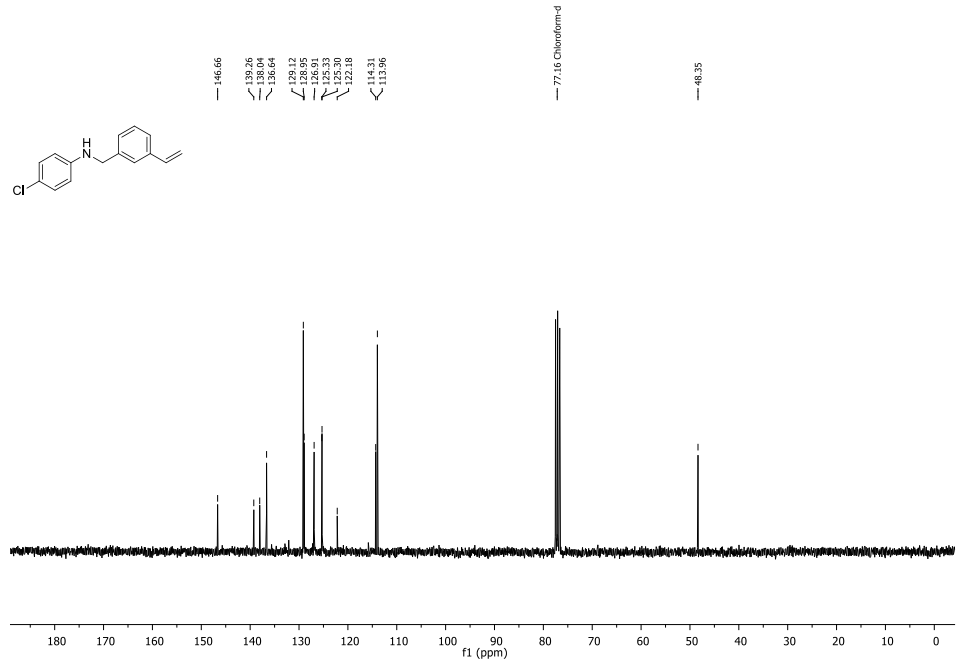
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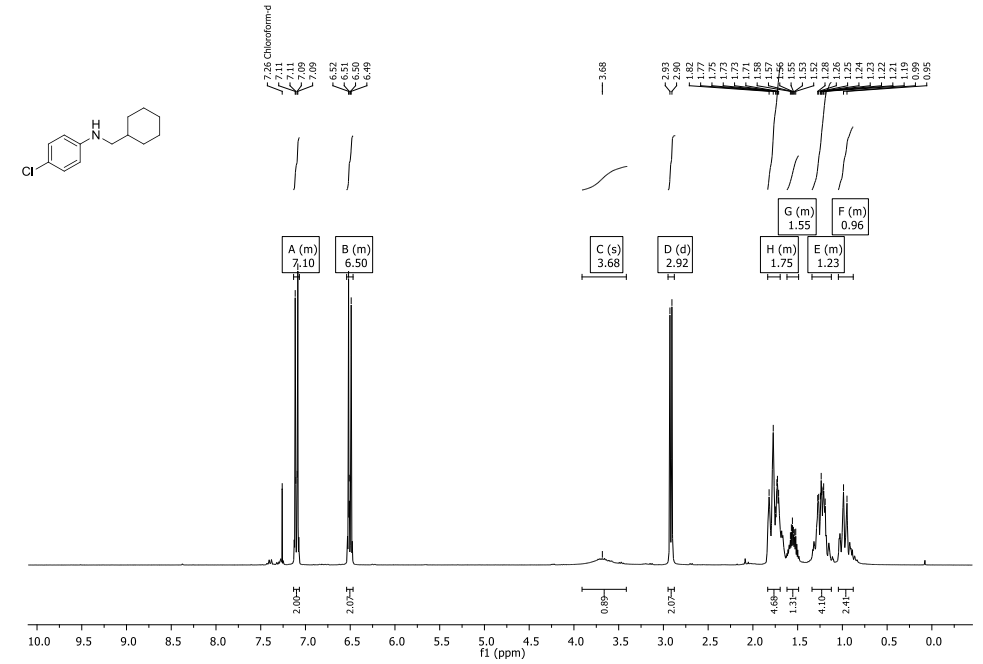
f1 (ppm)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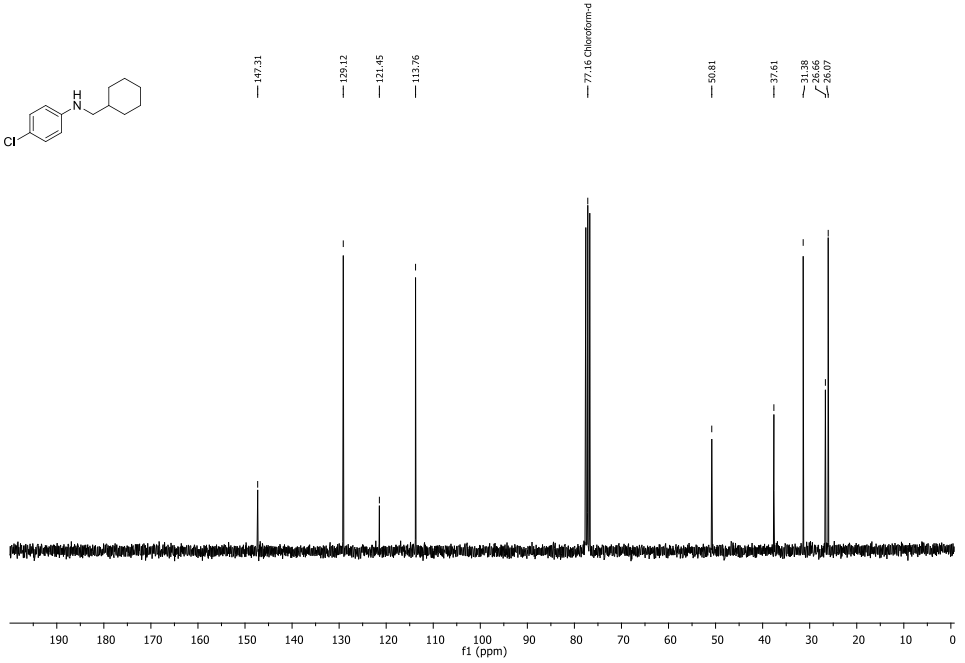
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f1 (ppm)

6

Efficient and selective *N*-methylation of nitroarenes under mild reaction conditions

6. Efficient and selective *N*-methylation of nitroarenes under mild reaction conditions
    6.1. Manuscript
    6.2. Supporting Information

"Me enseñaron que el camino del progreso no es ni rápido ni fácil."

Marie Curie

Efficient and Selective *N*-Methylation of Nitroarenes under Mild Reaction Conditions

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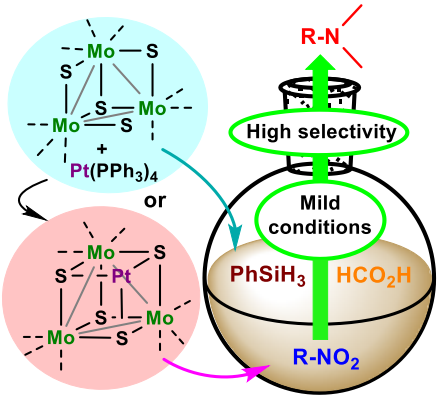
(Accepted with revisions in ***Chemistry-A European Journal****)*



Direct and mild *N*-methylation: Nitroarenes have been smoothly methylated using formic acid as a C_1 source and phenylsilane as reducing agent. In the presence of cubane-type complexes (see scheme) tertiary amines have been obtained at mild conditions with good functional group tolerance.

Abstract

Herein, we report a straightforward protocol for the preparation of *N*,*N*-dimethylated amines from readily available nitro starting materials using formic acid as a renewable C_1 source and silanes as reducing agents. This tandem process is efficiently accomplished in the presence of a cubane-type Mo_3PtS_4 catalyst. For the preparation of the novel $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ (**3**$^+$) (dmen: *N*,*N'*-dimethylethylenediamine) compound we have followed a [3 + 1] building block strategy starting from the trinuclear $[Mo_3S_4Cl_3(dmen)_3]^+$ (**1**$^+$) and $Pt(PPh_3)_4$ (**2**) complexes. The heterobimetallic **3**$^+$ cation preserves the main structural features of its **1**$^+$ cluster precursor. Interestingly, this catalytic protocol operates at room temperature with high chemoselectivity when the **3**$^+$ catalysts co-exists with its trinuclear **1**$^+$ precursor. *N*-heterocyclic arenes, double bonds, ketones, cyanides and esters functional groups are well retained after *N*-methylation reaction of the corresponding functionalized nitroarenes. In addition, benzylic-type nitro compounds can also be methylated following this protocol.

Introduction

N-methylated amines are widely used as platform chemicals for the preparation of medicines, pesticides, dyes and perfumes.[1] Traditional procedures for *N*-methylation of amines in fine chemical manufacture rely on reductive amination reactions using toxic formaldehyde as C_1 source,[2] whereas carcinogenic methylating reagents, such as methyl iodide, methyl trifluoromethanesulfonate, dimethyl sulfate or diazomethane are still popular at laboratory scale.[3] Hence, there exists growing interest in the search for greener and safer C_1 feedstocks for *N*-methylations in industry and academia. In recent years, great progress has been made by using CO_2,[4] dimethyl carbonate,[5] formic acid (FA),[6] methanol[7] or dimethylsulfoxide[8] as methylating reagents. Among them, FA is an attractive reagent to introduce carbon into amines.[9] FA is a non-toxic and biodegradable liquid produced industrially by

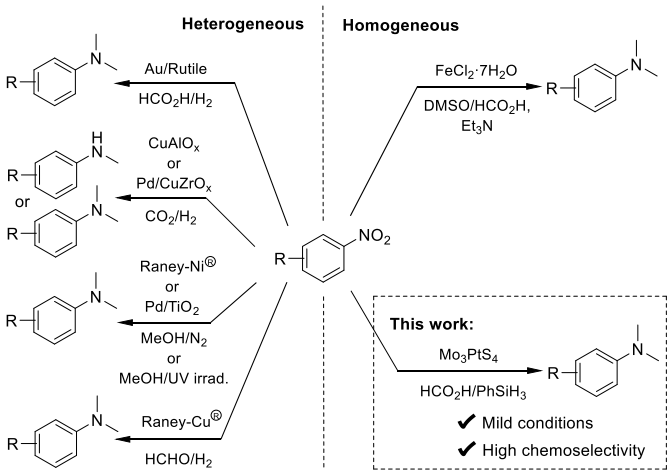
hydrolysis of methyl formate or by CO_2 hydrogenation, and is one of the major by-products of lignocellulosic biomass processing.[10] Furthermore, FA represents an ideal liquid hydrogen carrier for renewable energy storage,[11] and has been thoroughly investigated as a liquid surrogate of molecular hydrogen for the well-established transfer hydrogenation reactions.[12]

Pioneering work on *N*-methylation of amines with FA as a C_1 building block was reported by some of us using silanes as reducing agents in the presence of an *in situ* combination of the commercially available Karstedt's catalyst and dppp (1,3-bis(diphenylphosphino)propane) as ligand.[6a] Notably, by using a related Pt/diphosphine-based catalyst the protocol was also extended to higher carboxylic acids (RCO_2H; $R \neq H$) to give a broad range of secondary and tertiary amines.[13] This work was followed by others who have expanded the range of homogeneous catalysts available to Ir,[14] Rh,[4s] Ru,[15] and Cu,[6h] as well as to a heterogeneous Pt/C catalyst for the construction of the C-N bond employing hydrosilanes as reductants.[6g] In this context, the metal-free amine alkylation reaction using $B(C_6F_5)_3$ as catalyst is also noteworthy.[6e, 6f] Cantat *et al.* first,[6b] and Kim *et al.*[6c] reported the *N*-methylation of amines applying FA as a unique carbon and hydrogen source catalyzed by a Ru/Triphos [Triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane] complex or a heterogeneous PdAg alloy catalyst, respectively. Furthermore, the Ru/Triphos system has also proven to be an excellent catalyst for the *N*-alkylation of amines with a variety of carboxylic acids using molecular hydrogen as reducing agent.[16]

Although tremendous success has been achieved in the search for greener methylating reagents, the development of new strategies to access *N*-methylated amines from readily available feedstocks in a safe, compact and energy-efficient manner still remains as a major challenge. Typically, their preparation involves synthesis and isolation of the amine, followed by *N*-methylation in two separated

individual stages. In this respect, the design of a domino or tandem process that avoids the synthesis and isolation of the amine intermediate is clearly advantageous.

Currently, one of the most common methodologies to access (aromatic) amines is the reduction of nitro compounds,[17] and thus the development of a straightforward reductive methylation of nitroarenes is of great practical significance. However, only a few examples, mostly using heterogeneous catalysts, dealing with this convenient and direct strategy have been reported to date (Scheme 1). In 2009, Li *et al.* achieved the synthesis of *N*,*N*-dimethylaniline from nitrobenzene and methanol over a pretreated Raney-Ni® catalyst under high temperature and N_2 pressure (170 ºC; 30 bar N_2).[7c] In 2013, Rong *et al.* reported the use of a skeletal Cu (also known as Raney-Cu®) catalyst for the direct *N*-methylation from nitroarenes, but toxic and carcinogenic formaldehyde was employed as C_1 source in the presence of molecular hydrogen.[18] Notably, Shi *et al.* described the synthesis of a limited number of *N*-methylated anilines from nitroarenes employing CO_2/H_2 and $CuAlO_x$ or $Pd/CuZrO_x$ as catalysts under harsh conditions and long reaction times (150-170 ºC, 35-100 bar; 30-48 h).[4j, 4k] Soon after, the same group accomplished the direct *N*-methylation of nitroarenes using methanol and TiO_2-supported nanopalladium catalysts (Pd/TiO_2) at room temperature, albeit photoactivation under intense UV irradiation was required.[7g] Later, Cao *et al.* utilized a Au/rutile catalyst that allowed the preparation of *N*,*N*-dimethylanilines from nitroarenes using formic acid (FA) as benign C_1 source, but high pressure of H_2 (40 bar) and high temperature (140 ºC) were required to avoid accumulation of intermediate products.[6d] Unfortunately, the application of all these methods, especially at laboratory scale, is constrained by the needs of high temperatures, special high-pressure equipment and/or hazardous UV irradiation. In addition, they present a limited substrate scope and their functional-group tolerance to other reducible functionalities has been scarcely investigated.



Scheme 1. Direct one-pot *N*-methylation of nitroarenes.

In this regard, homogeneous catalysis should provide a more convenient approach to obtain a broad functional group tolerance and high activity under mild conditions. Wang and Xiao *et al.* have recently reported a Fe-catalyzed *N*-methylation of nitroarenes under transfer hydrogenation conditions using dimethylsulfoxide (DMSO) and a mixture of FA/Et_3N as methylating and reducing agents, respectively (Scheme 1).[8] However, the required temperature (150 ºC) is still too high and the functional-group tolerance to sensitive moieties, such as double bonds, ketones or carboxylic acid derivatives, has not been demonstrated. Hence, the development of a chemoselective catalytic protocol for *N*-methylation of nitroarenes that operates under mild conditions is still highly desirable. A key prerequisite for such pursuit lies in the proper choice of a catalyst able to lead to the direct one-pot C-N bond construction in a domino or tandem sequence. In this sense, the design of heterobimetallic complexes with several active sites acting individually or in a cooperative manner to catalyze the individual steps of the overall catalytic process is an attractive approach.

Since many years, one of our groups has been involved in the preparation of heterobimetallic cuboidal $Mo_3M'S_4$ clusters by incorporation of a second transition metal atom (M') into trinuclear Mo_3S_4 complexes.[19] The resulting $Mo_3M'S_4$ cluster unit displays a cubane-type structure where the metals and sulfur atoms occupy adjacent vertices in a cube (Figure 1). In general, their application as catalysts for organic synthesis is quite limited and most of their reported activity relies on the heterometal (M' = Pd,[20] Ni,[21] Ru,[22] and Cu[19e, 19h]).[23]

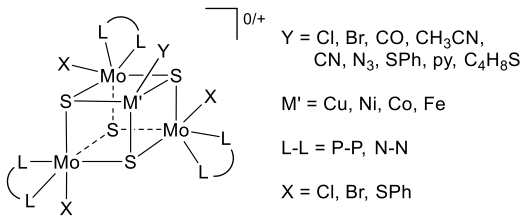


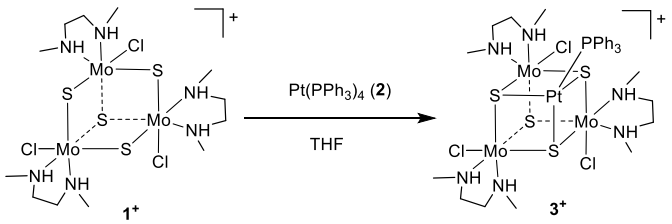
Figure 1. Cubane-type $Mo_3M'S_4$ clusters.

In the last few years, we have demonstrated that incomplete cubane-type Mo_3S_4 complexes functionalized with diphosphine, diamine or diimine ligands are excellent chemoselective catalysts for the reduction of nitroarenes using different reducing agents.[12e, 24] In addition, some of us have also recently applied Pt-based catalysts to establish new efficient synthetic routes for *N*-alkylation of amines.[5g, 6a, 13] This experience inspired us to prepare a heterobimetallic Mo_3PtS_4 cluster and explore its performance as catalyst for the direct one-pot reductive methylation of nitroarenes under mild conditions using FA as C_1 source and silanes as reducing agents.

Results and Discussion

Synthesis and characterization of the catalyst

Incomplete cubane-type Mo_3S_4 clusters are known to act as metalloligands towards a second transition or post-transition metal to form a large family of heterobimetallic cuboidal $Mo_3M'S_4$ complexes both in aqueous and organic media.[19b, 23, 25] This synthetic approach, so-called [3 + 1] building block strategy, has proven to be an efficient route to construct Mo_3PtS_4 clusters by reaction of the preassembled Mo_3S_4 complex containing aqua, diphosphine or methylcyclopentadienyl ligands with either Pt(0) complexes or Pt(II) salts, the latest in the presence of a strong reducing agent.[26] In this work, this synthetic strategy has been extended to the diamino Mo_3PtS_4 system. Reaction of the $[Mo_3S_4Cl_3(dmen)_3]^+$ (**1**$^+$) cation with the mononuclear complex $Pt(PPh_3)_4$ (**2**) at room temperature in THF, readily affords the heterobimetallic complex $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ (**3**$^+$) as represented in Scheme 2.



Scheme 2. Synthetic procedure for the preparation of $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ (**3**$^+$).

Tetrafluoroborate salts of **3**$^+$ were isolated as a brown air-stable solid in 52% yield. Single crystals were obtained by slow diffusion of diethyl ether into dichloromethane sample solutions. The structure of **3**(BF_4) was determined by single crystal X-ray diffraction methods and its ORTEP representation with the most relevant bond distances is depicted in Figure 2. The cluster is formed by a single cubane-like Mo_3PtS_4 array, in which the metal atoms occupy the vertices of a slightly

distorted tetrahedron and each tetrahedron face is capped by a μ_3-coordinated sulfur atom. Each molybdenum atom presents an octahedral coordination environment with the outer position occupied by one chlorine and two nitrogen atoms of the diamine ligand while platinum possess a tetrahedral coordination with the outer position occupied by the phosphorous atom of the triphenylphosphine ligand. In general, cation **3**$^+$ shares the main geometric features with other cubane-type Mo_3PtS_4 complexes reported to date.[26]

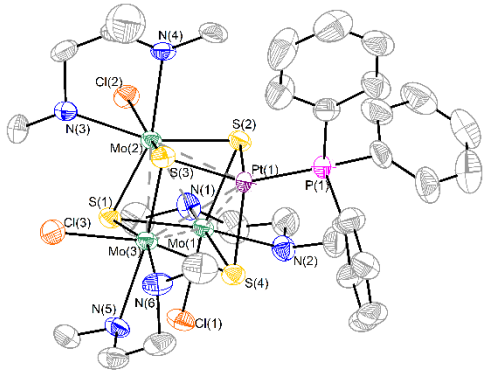


Figure 2. ORTEP representation (50% probability level ellipsoids) of the cationic cluster **3**$^+$. Hydrogen atoms are omitted for clarity. Selected averaged bond lengths (Å): Mo-Mo 2.775[6], Mo-Pt 2.836[4], Mo-(μ_3-S(1)) 2.333[1], Mo-(μ_3-S)$_{trans\text{-}Cl}$ 2.352[2], Mo-(μ_3-S)$_{trans\text{-}N}$ 2.352[7], Mo-N$_{(trans\text{-}S(1))}$ 2.278[8], Mo-N$_{(cis\text{-}S(1))}$ 2.291[3], Mo-Cl 2.517[10], Pt-P 2.262(2) and Pt-(μ_3-S) 2.354[4].

Cationic cluster **3**$^+$ preserves the idealized C_3 symmetry of its **1**$^+$ precursor and it is conveniently identified in solution by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy region (Figures SI1 and SI2 in the Supporting Information) Further support on the integrity of complex **3**(BF_4) in solution is provided by ESI mass spectrometry where a peak centred at m/z = 1244.8 is associated to the pseudomolecular **3**$^+$ cation on the basis of the m/z value and its characteristic isotopic pattern (Figure SI3 in the Supporting Information).

Upon Pt insertion, the electron precise $Mo_3S_4^{4+}$ unit with six metal cluster skeletal electrons (CSE) to form three metal-metal bonds, becomes a $Mo_3PtS_4^{4+}$ cluster containing sixteen CSE, and so some changes in their redox properties are expected. The electronic delocalization in the resulting heterobimetallic systems makes inconclusive all schemes directed towards the metal oxidation states assignment.[19g] Electrochemical properties of the incomplete **1**$^+$ and cubane-type **3**$^+$ complexes have been investigated by cyclic voltammetry (see Table 1 and Figure SI4 in the Supporting Information). Complex **3**$^+$ undergoes one reduction and one oxidation quasireversible processes of similar intensity at -1,02 and 1.10 V, respectively, a redox behavior similar to that reported for the $[Mo_3PtS_4(\eta^5\text{-}Cp')_3(PPh_3)]^+$ (Cp' = methylcyclopentadienyl) ion complex.[27] The cyclic voltamogram of the trinuclear **1**$^+$ precursor shows a unique quasireversible reduction wave at -0,45 V while no oxidation process is observed within the solvent window. Therefore, incorporation of the Pt-PPh_3 fragment into the Mo_3S_4 core to give the heterobimetallic complex **3**$^+$ exerts an important electronic effect, making the heterobimetallic cluster more difficult to reduce and easier to oxidize than its trinuclear precursor, as observed for the Pt insertion into the cyclopentadienyl Mo_3S_4 complex.[27]

Table 1. Redox potentials of **1**$^+$ and **3**$^+$ clusters in dichloromethane[a]

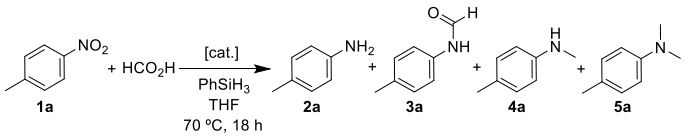
Compound	Oxidation	Reduction
	$E_{1/2}$[b](ΔE[c]) (V)	$E_{1/2}$[b](ΔE[c]) (V)
1(BF_4)	-	-0.45(0.13)
3(BF_4)	1.15(0.06)	-1.02(0.08)

[a] $E_{1/2}$ (Fc/Fc^+) = 0.44 V (*vs* Ag/AgCl). [b] Potentials measured at 100 mV/s. [c] ΔE = |Ea - Ec|

Catalytic results

The catalytic activity of the heterobimetallic **3**(BF_4) cluster in the direct *N*-methylation of nitroarenes was investigated in the model reaction of *p*-nitrotoluene (**1a**) with formic acid and using phenylsilane as reductant. Initial experiments were conducted in tetrahydrofurane at 70 ºC in the presence of different catalyst loadings. Almost full conversion with formation of the desired *N*,*N*-dimethyl-*p*-toluidine (**5a**) as main product was achieved with 1 mol% of the heterobimetallic **3**(BF_4) cluster (Table 2, entry 1). In addition, small amounts of *p*-toluidine (**2a**) and the monomethylated *N*-methyl-*p*-toluidine (**4a**) were also detected. To our delight, an increase of catalyst loading up to 3 mol% affords almost a quantitative yield of **5a** (97%) after 18 h (Table 2, entry 2). At shorter reaction times (8 h), **1a** was partially converted and the dimethylated amine **5a** was obtained in a 33% yield (Table 2, entry 3). Incidentally, the $\mathbf{3}^{+}$ cluster still remains in the reaction mixture as evidenced by electrospray ionization mass spectrometry (ESI-MS) measurements (Figure SI5 in the Supporting Information). No reaction took place in the absence of phenylsilane even when a large excess of formic acid (Table 2, entry 4) or formic acid and triethylamine mixtures (Table 2, entries 4-5) were employed. Likewise, the use of other hydrosilanes or solvents led to much lower reactivity towards the formation of the desired dimethylated product 5a (Tables SI1 and SI2 in the Supporting Information).

Table 2. Optimization conditions of the *N*-methyalation of nitroarenes.[a]



Entry	Catalyst	Catalyst loading (mol%)	Conv. [%][b]	Yield [%][b] 2a	3a	4a	5a
1	**3**(BF_4)	1	90	15	0	16	40
2	**3**(BF_4)	3	>99	1	0	2	97
3[c]	**3**(BF_4)	3	83	19	0	14	33
4[d]	**3**(BF_4)	3	0	0	0	0	0
5[e]	**3**(BF_4)	3	0	0	0	0	0
6	**1**(BF_4)	5	>99	1	51	0	38
7	**2**	5	89	30	0	7	27
8[c]	**1**(BF_4):**2**	3:3	>99	2	1	1	87
9[c]	**1**(BF_4):**2**	3:1	>99	2	1	1	90
10[f]	**1**(BF_4):**2**	3:1	>99	0	2	1	89
11[f]	**3**(BF_4)	3	5	1	0	1	3

[a] Reaction conditions: **1a** (0.1 mmol), HCO_2H (8.5 equiv.), $PhSiH_3$ (10 equiv.), THF (2 mL). [b] Determined by GC using *n*-hexadecane as an internal standard. [c] 8 h. [d] Without silane; 26 equiv. HCO_2H. [e] Without silane; HCO_2H/Et_3N (26/21 equiv.). [f] 25 ºC.

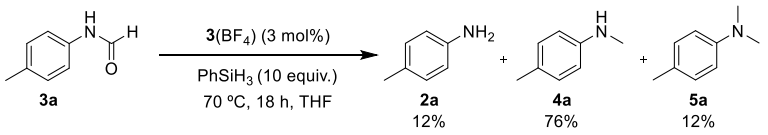
Next, we explored the catalytic activity of the precursor complexes, $Pt(PPh_3)_4$ (**2**) and the trinuclear **1**(BF_4), used for the preparation of the heterobimetallic **3**(BF_4) cluster. These complexes are known to be effective catalysts for the *N*-methylation of amines as well as for the reduction of nitroarenes, respectively,[6a, 24a] so direct *N*-methylation of nitroarenes catalyzed by any of these precursors should not be discarded. However, complexes **1**(BF_4) and **2** resulted to be less efficient catalysts

than the heterobimetallic **3**(BF_4) cluster affording low yields of the dimethylated amine **5a** (Table 2, entries 6-7).

Then, we decided to explore the catalytic activity of the *in situ* generated **3**$^+$ cluster using different ratios between the trinuclear **1**(BF_4) cluster and the mononuclear $Pt(PPh_3)_4$ (**2**) complex. When the direct *N*-methylation of **1a** was carried out in the presence of equimolecular mixtures of **1**(BF_4) (3 mol%) and **2** (3 mol%) an excellent yield of **5a** was achieved after 8 h (Table 2, entry 8). Interestingly, the platinum complex loading could be decreased up to 1 mol% without any loss in conversion and yield (Table 2, entry 9). It should be noted that in the presence of a 3-fold excess of the trinuclear complex **1**(BF_4) with respect to **2**, platinum is fully incorporated into the Mo_3S_4 cluster core thus producing a mixture of cluster complexes **3**(BF_4) and **1**(BF_4) as evidenced by ESI-MS (Figure SI6 in the Supporting Information). After completion of the catalytic reaction (8 h), the peaks associated to the tri- and tetranuclear clusters are still present in the ESI-MS spectrum. Unfortunately, all efforts to detect any potential silylated species generated during the catalytic reaction were unsuccessful, likely due to strong ion-suppression effects.[28]

Remarkably, the presence of the trinuclear **1**$^+$ cluster has a positive effect on the process not only lowering reaction times but also allowing the reaction to proceed at room temperature. (Table 2, entry 10) In fact, direct *N*-methylation of the nitroarene **1a** is successfully accomplished at room temperature when both clusters **1**$^+$ and **3**$^+$ are present while complex **3**$^+$ alone is inactive under these conditions (Table 2, entries 10 and 11, respectively). However, the aniline **2a** is efficiently methylated at room temperature in the presence of the heterobimetallic **3**$^+$ complex to afford the dimethylated product **5a** in 94% yield. These results suggest that the trinuclear **1**$^+$ complex is more efficient catalyst than **3**$^+$ for the nitroarene to aniline conversion, that is the first step of this tandem process.

With respect to the reaction mechanism, in order to clarify the elementary steps involved in the direct *N*-methylation of nitroarenes, we performed the reduction of the intermediate *p*-methylformanilide (**3a**) with phenylsilane in the absence of formic acid. As shown in Scheme 3, the expected monomethylated aniline **4a** was afforded as major product (76%), but also **2a** and the dimethylated aniline **5a** were formed in 12% yield. As it has been already reported, a rational route for the formation of **5a** in the absence of formic acid should involve condensation of the initially formed **4a** and the starting formamide **3a** to produce the corresponding urea derivate, followed by reduction of this intermediate.[6a] Hence, the direct *N*-methylation of nitroarenes under our reaction conditions involves formation of the primary aniline by reduction of the starting nitroarene and methylation reaction with formic acid, which proceeds through the formation of formamide and urea derivatives as reaction intermediates (Scheme SI1 in the Supporting Information).

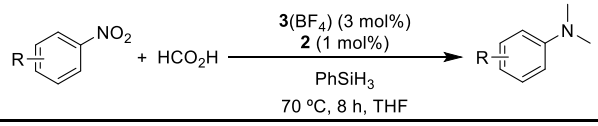


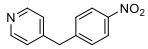
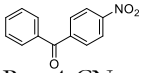
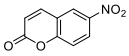
Scheme 3. Control experiment: reduction of *p*-methylformanilide (**3a**)

Next, the potential of this catalytic protocol for the direct *N*-methylation of nitroarenes was further investigated. For convenience, the mixture of the trinuclear **1**(BF_4) (3 mol%) and the mononuclear **2** (1 mol%) complexes combined *in situ* was used as catalyst. Apart from the benchmark substrate, **1a**, two nitroarenes containing electron-donating substituents, such as methoxy or thiomethyl groups, were also smoothly methylated affording the corresponding dimethylated anilines in 74 and 94% yield, respectively (Table 3, entries 1-2). In the absence of any substituent on the aromatic ring, the *N*-methylation reaction also proceeded efficiently under otherwise the same reaction conditions (Table 3, entry 3). Notably, halide-containing nitroarenes were also fully converted to the corresponding halogen-substituted

dimethylated products in 80-99% yields. It should be noted that no dehalogenation processes were observed in any case (Table 3, entries 4-8).

Table 3. Direct *N*-methylation of nitroarenes with formic acid.[a]

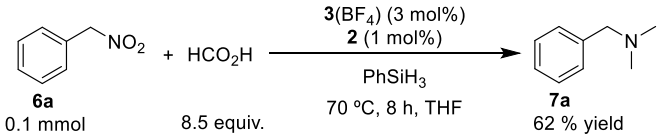


Entry	Substrate	Conv.[b]	Yield[b]
1	R = 3-OMe	>99	74
2	R = 4-SMe	>99	(94)
3	R = H	>99	91
4	R = 4-F	>99	86
5	R = 3-Cl	>99	96 (88)
6	R = 2-Cl	>99	>99
7	R = 4-Br	>99	97
8	R = 3-I	>99	80
9[c]		>99	(72)
10[d,e,f]	R = 3-$CHCH_2$	>99	(73)
11[g]		>99	96
12[e,h]	R = 4-CN	>99	66
13[g]	R = 4-CO_2Me	>99	(89)
14[c,g]		>99	(83)

[a] Reaction conditions: Nitroarene (0.1 mmol), HCO_2H (8.5 equiv.), $PhSiH_3$ (10 equiv.), THF (2 mL). [b] Determined by GC using *n*-hexadecane as an internal standard; yields of isolated products given in parentheses [c] Monomethylated amine as by-product. [d] 18 h, 25 ºC. [e] Traces of monomethylated amine. [f] Traces of 3-ethyl-*N*,*N*-dimethylaniline. [g] HCO_2H (15 equiv.). [h] *N*,*N*-dimethyl-*p*-toluidine as by-product.

More interestingly, *N*-methylation of more challenging nitroarenes containing other easily reducible functional groups was also successfully accomplished (Table 3, entries 10-14). *N*-heterocyclic arenes, double bonds, ketones as well as carboxylic acid derivatives, such as cyanides and esters functional groups were well retained in the final dimethylated anilines which were obtained in good to excellent yields. In some of these cases, room temperature (Table 3, entry 10), increased amounts of formic acid and/or reaction time (Table 3, entries 11,13-14) were required to get optimal yields.

With good reactivity for *N*-methylation of aromatic nitroarenes, we became interested in exploring the ability of this catalytic system to methylate benzylic-type nitro compounds. As shown in Scheme 3, phenylnitromethane (**6a**) was used as substrate under optimized reaction conditions affording *N*,*N*-dimethylbenzylamine (**7a**) in 62% yield without detection of any other by-products.



Scheme 4. *N*-methylation of phenylnitromethane.

Conclusions

In summary, we have developed a convenient and straightforward catalytic protocol for the preparation of *N*,*N*-dimethylated amines from readily available nitroarenes using formic acid as a renewable C_1 source and silanes as reducing agents. As catalyst to accomplish this domino reaction, we have designed a heterobimetallic cubane-type Mo_3PtS_4 cluster. By applying the heterobimetallic **3**(BF_4) complex the direct *N*-methylation of nitroarenes has been smoothly accomplished under mild conditions (70 ºC, ambient pressure). Interestingly, we have demonstrated that in this reaction sequence the presence of the trinuclear complex **1**(BF_4) favors the first step, that is

the nitroarene to aniline transformation, so almost quantitative yields of the *N,N*-methylated amine can be achieved even at room temperature and/or lowering the reaction times. Notably, the catalytic protocol has been applied to nitroarenes containing easily reducible functionalities, such as *N*-heterocyclic arenes, double bonds, ketones, cyanides and esters functional groups that are well retained in the final dimethylated anilines. Furthermore, benzylic-type nitro compounds are potential candidates to be directly methylated under this protocol.

In general, its operational simplicity with no need to use any special high-pressure equipment, the mild reaction conditions (room temperature), the use of readily available feedstocks and its high chemoselectivity make this protocol an attractive and useful methodology for organic synthesis.

Experimental Section

General remarks

All reactions were carried out under a nitrogen atmosphere using standard Schlenck techniques. The trinuclear complex $[Mo_3S_4Cl_3(dmen)_3]BF_4$ (**1**(BF_4)) was prepared according to the literature procedure.[24b] $Pt(PPh_3)_4$ (**2**) was pursued from commercial sources and used as received.

Physical measurements

Elemental analyses were carried out on a EuroEA3000 Eurovector Analyser. Electrospray mass spectra were recorded with a Quattro LC (quadrupole-hexapole-quadrupole) mass spectrometer with an orthogonal Z-spray electrospray interface (Micromass, Manchester, UK). The cone voltage was set at 20 V unless otherwise stated using CH_3CN as the mobile phase solvent. Sample solutions have been infused via syringe pump directly connected to the ESI source at a flow rate of 10 μL/min

and a capillary voltage of 3.5 kV was used in the positive scan mode. Nitrogen was employed as drying and nebulizing gas. Isotope experimental patterns were compared with theoretical patterns obtained using the MassLynx 4.1 program.[29] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 MHz or 300 MHz spectrometers using CD_2Cl_2 or $CDCl_3$ as solvents. Gas chromatography analyses were performed on an Agilent 7820A GC System equipped with a FID and a capillary column Agilent (HP-5, 30m x 0.32mm x 0.25 μm). Mass determination was carried out on a GC-Mass Agilent 5977E network equipped with a mass-selective detector. Cyclic voltammetry experiments were performed with an Echochemie Pgstat 20 electrochemical analyzer. All measurements were carried out with a conventional three-electrode configuration consisting of glassy carbon working and platinum auxiliary electrodes and an Ag/AgCl reference electrode. The solvent used was dichloromethane (HPLC grade) which was deoxygenated before used and tetrabutylammonium hexaflurophosphate (0.1 M solution) was used as supporting electrolyte.

Catalyst preparation

Synthesis of $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]BF_4$ ($3(BF_4)$): To a green solution of the trinuclear complex $1(BF_4)$ (100 mg, 0.114 mmol) in dry THF (10 mL) was added a two-fold excess of the mononuclear Pt complex 2 (285 mg, 0.229 mmol) under inert atmosphere. The reaction occurs with an immediate colour change to brown and the formation of a precipitate. After stirring the reaction mixture for 24 h at room temperature, the solid was separated by filtration, washed with cold THF and dissolved in dichloromethane. Finally, the product was crystallized from dichloromethane/ether mixtures to afford a dark-brown solid characterized as $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]BF_4$ ($3(BF_4)$) (80 mg, 52 % yield). Elemental analysis for $3(BF_4)\cdot Et_2O$: calc. (%) for $Mo_3PtPS_4Cl_3N_6C_{34}H_{61}OBF_4$: C 29.06, H 4.38, N 5.98, S

9.13; found (%): C 29.20, H 4.42, N 5.9, S 9.13. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.77 – 7.18 (m, 15H, CH), 4.25 (br s, 3H, NH), 4.15 (br s, 3H, NH), 3.30 – 3.12 (m, 6H, CH_2), 2.98 (d, *J* = 5.6 Hz, 9H, CH_3), 2.93 – 2.70 (m, 6H, CH_2), 2.14 (d, *J* = 6.1 Hz, 9H, CH_3); ^{13}C NMR (101 MHz, CD_2Cl_2) δ [134.31, 134.18 (C, d, $^{1}J_{C\text{-}P}$ = 12.34 Hz)]), [132.54, 132.44 (CH, d, $^{3}J_{C\text{-}P}$ = 9.41 Hz)], [131.69, 131.67 (CH, d, $^{4}J_{C\text{-}P}$ = 2.47 Hz)], [129.27, 129.15 (CH, d, $^{2}J_{C\text{-}P}$ = 11.37 Hz)], 56.69 (s, CH_2), 52.49 (s, CH_2), 47.52 (s, CH_3), 43.82 (s, CH_3); ESI-MS (CH_3CN, 20 V): *m*/*z* 1244.8 [M^+].

Catalytic activity tests

General procedure for the direct *N*-methylation of *p*-nitrotoluene (1a): Under a nitrogen atmosphere, $PhSiH_3$ (123 μL, 1 mmol), 1a (13.7 mg, 0.1 mmol), hexadecane (15 μL; added as an internal standard) and HCO_2H (32 μL, 0.85 mmol) were added to a brown solution of 3(BF_4) (4 mg, 0.003 mmol) in dry THF. After the reaction mixture was stirred for 18 h at 70 ºC, ethyl acetate (5 mL) was added and a sample for GC was taken after slow addition of NaOH solution (3 M (aq.), 2 mL) and vigorous stirring for 3 h at room temperature. All catalytic reactions were performed at least twice to ensure reproducibility. To determine the isolated yield of the methylated amines, no internal standard was added. After completion, dilution with ethyl acetate and stirred for 3 h with the aqueous solution of NaOH, the mixture was extracted with ethyl acetate (three times) and the combined organic layers were dried over $MgSO_4$ anhydrous. Finally, the organic phase was filtered, concentrated and purified by preparative thin layer chromatography (*n*-hexane/ethyl acetate mixtures) to give the corresponding dimethylated amines.

When a mixture of the trinuclear 1(BF_4) and the mononuclear 2 complexes mixed *in situ* was used as catalyst, the procedure for *N*- methylation of nitroarenes was as follows: Under a nitrogen atmosphere, complex **2** (1.3 mg, 0.001 mmol) was added to a green solution of **1**(BF_4) (2.6 mg, 0.003 mmol). Immediately, the solution

colour changed to brown greenish. After stirring for 10 min at room temperature, the general procedure described above was applied.

X-ray data collection and structure refinement

Slow vapor diffusion of diethyl ether into a sample solution of **3**(BF_4) in CH_2Cl_2 afforded brown needle-shaped crystals suitable for X-ray studies. Diffraction data collection was performed at 200 K on an Agilent Supernova diffractometer equipped with an Atlas CCD detector using Mo-Kα radiation (λ = 0.71073 Å). No instrument or crystal instabilities were observed during data collection. Absorption correction based on the Multi-scan method was applied.[30-31] The structure was solved by direct methods and refined by the full-matrix methods based on F^2 with the program SHELXL-13 using the Olex2 software package.[32-33] The structural figure was drawn using the Diamond visual crystal structure information system software.[34] Crystal data for **3**(BF_4)·O(CH_2CH_3): $C_{34}H_{51}BCl_3F_4Mo_3N_6OPPtS_4$; M = 1395.08; monoclinic; space group $P2_1/c$; a = 12.3842(4), b = 17.7628(6), c = 22.6052(13) Å; β = 91.909(4)°; V = 4969.9(4) Å^3; T = 200(14) K; Z = 4; μ($Mo_{k\alpha}$) = 3.956 mm^{-1}; $Dcalc$ = 1.865 g/cm^3. Reflections collected/unique = 40770/9758 (R_{int} = 0.058). The non-hydrogen atoms of the cluster and the counter anion were refined anisotropically whereas the hydrogen atoms were included at their idealized positions and refined as riders with isotropic displacement parameters assigned as 1.2 times the Ueq value of the corresponding bonding partner for CH, CH_2 and NH groups and 1.5 times for methyl groups. In the last Fourier map a highly disordered diethyl ether molecule was found. To model this disorder, the O-C and C-C bond distances were constrained to a fix value and isotropic thermal parameters for the C32, C33 and C34 ether atoms were fixed at 0.1. The hydrogen atoms of the disordered solvent molecule were not included in the model. The final refinement converged with R_1 = 0.0525 and wR_2 = 0.1414 for all reflections, GOF=1.065 and max./min. residual electron density =

2.32/-1.79 e·Å^{-3}. CCDC 1554979 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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Keywords: tandem catalysis • nitroarenes • methylation • formic acid/silanes • cubane-type clusters

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SUPPORTING INFORMATION

Efficient and Selective *N*-Methylation of Nitroarenes under Mild Reaction Conditions

Elena Pedrajas, Iván Sorribes*, Eva Guillamón, Kathrin Junge, Matthias Beller* and Rosa Llusar*

1. Catalyst characterization.

Figure SI1. ^{1}H NMR spectrum of the complex $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ $(3(BF_4))$ in CD_2Cl_2

Figure SI2. ^{13}C NMR spectrum of the complex $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ $(3(BF_4))$ in CD_2Cl_2.

Figure SI3. ESI mass spectrum of the complex $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ $(3(BF_4))$ in CH_3CN at 20 V.

Figure SI4. Cyclic Voltammogram recorded on a CH_2Cl_2 solution containing 3^+ (a) and 1^+ (b) at scan rate of 100mV/s (*vs* Ag/AgCl).

2. Conditions optimization for the *N*-methylation of *p*-nitrotoluene (1a).

Table SI1. Screening of silanes.

Table SI2. Influence of the solvent on the catalytic *N*-methylation of 1a.

3. ESI mass spectra from the reaction mixture during the *N*-methylation of 1a.

Figure SI5. ESI mass spectrum from the *N*-methylation reaction after 8 hours.

Figure SI6. ESI mass spectrum from the mixture of $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (1(BF4)) (0.003 mmol) and $Pt(PPh_3)_4$ (2) (0.001 mmol) in THF after 10 minutes stirring at room temperature.

4. Reaction pathway investigation.

Scheme SI1. Proposed pathways for the direct *N*-methylation of nitroarenes with formic acid.

5. Characterization data of isolated products.

6. References

7. ^{1}H NMR and ^{13}C NMR spectra of isolated products.

1. Catalyst characterization

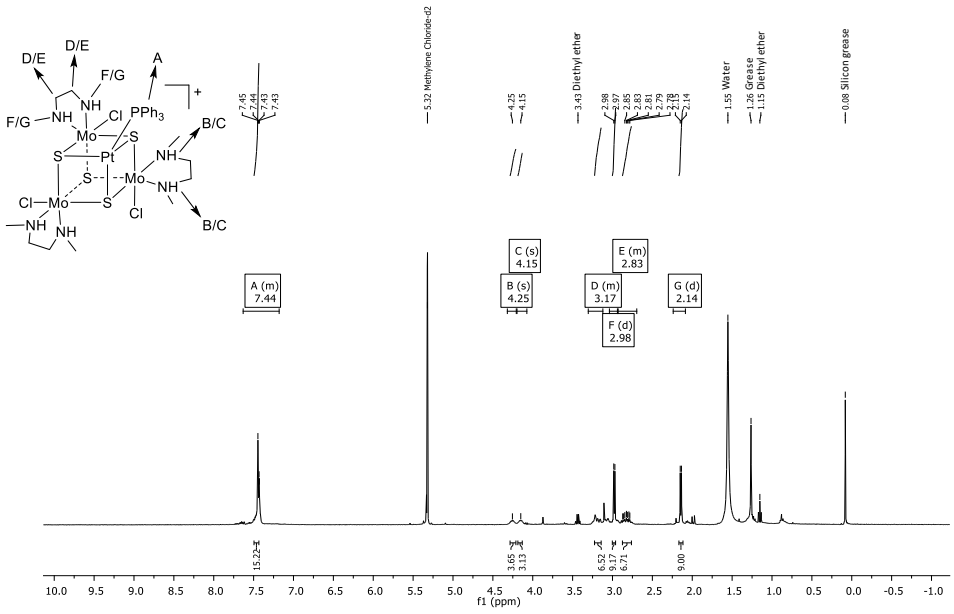


Figure SI1. ^{1}H NMR spectrum of the $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ (**3**(BF_4)) complex in CD_2Cl_2.

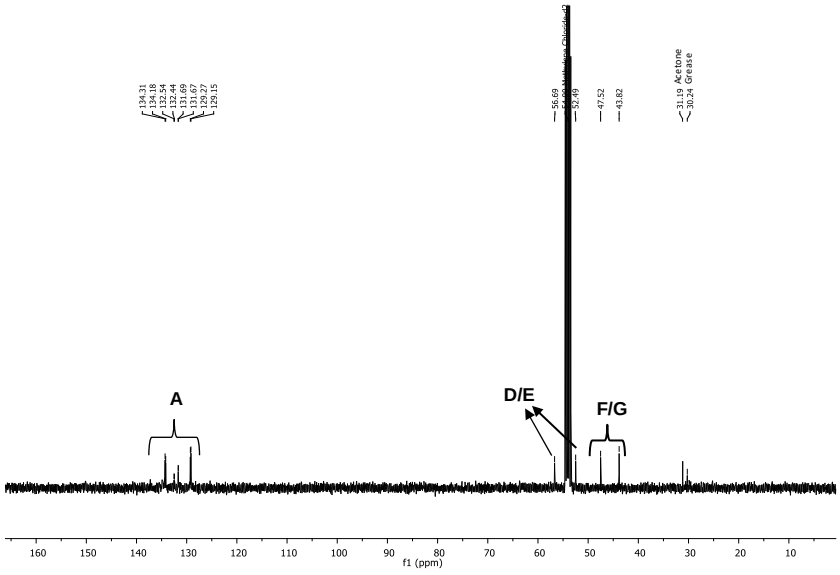


Figure SI2. ^{13}C NMR spectrum of the $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ (**3**(BF_4)) complex in CD_2Cl_2.

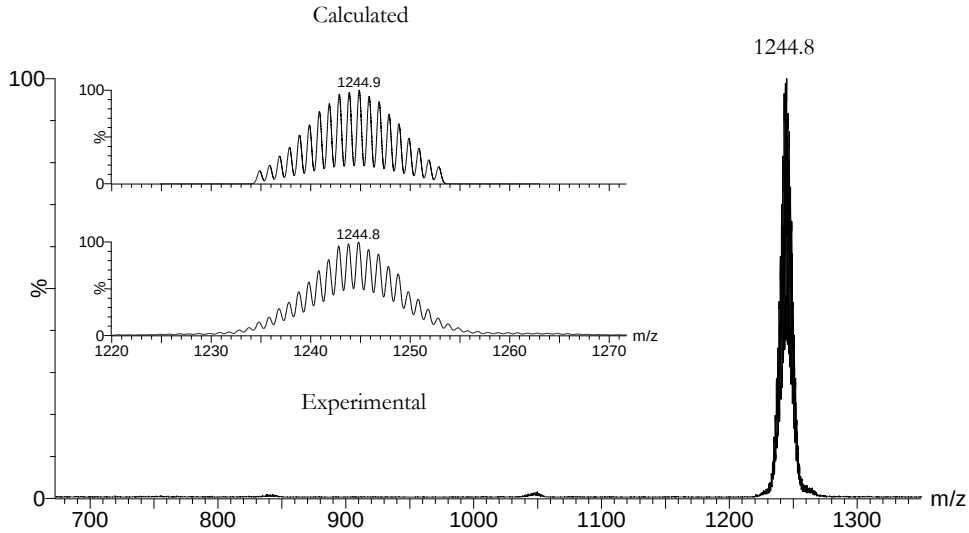


Figure SI3. ESI mass spectrum of the $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ complex (**3**(BF_4)) in CH_3CN at 20 V.

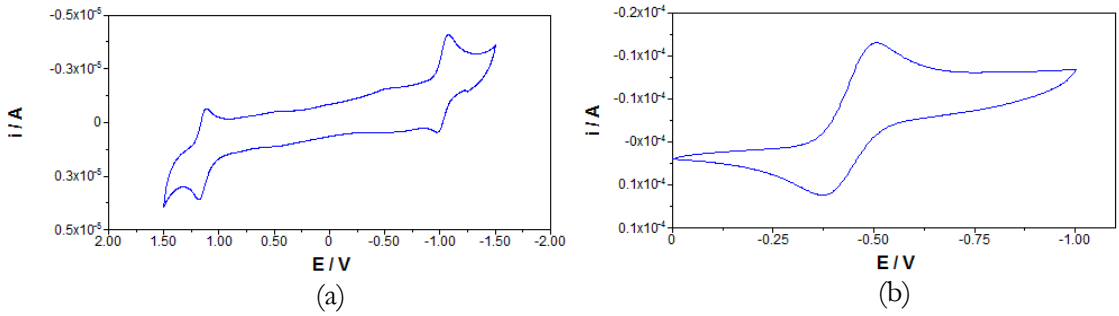
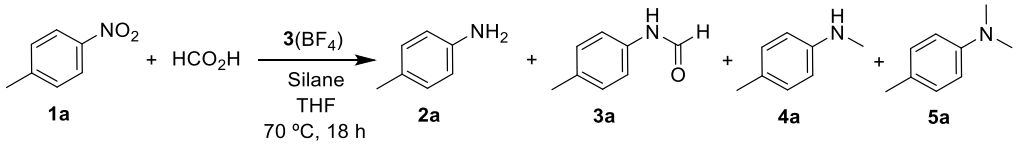


Figure SI4. Cyclic Voltammogram recorded on a CH_2Cl_2 solution containing $\mathbf{3}^+$ (a) and 1^+ (b) at scan rate of 100 mV/s (*vs* Ag/AgCl).

2. Conditions optimization for the *N*-methylation of *p*-nitrotoluene (1a).

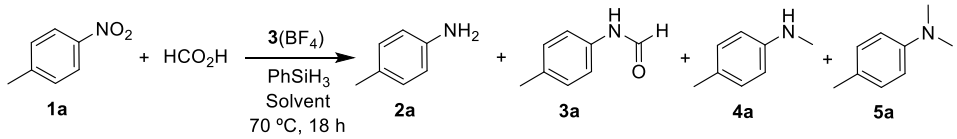
Table SI1. Screening of silanes.[a]



Entry	Silane	Conversion [%][b]	Yield **2a** [%][b]	Yield **3a** [%][b]	Yield **4a** [%][b]	Yield **5a** [%][b]
1	$PhSiH_3$	>99	1	0	2	97
2	Ph_2SiH_2	34	4	6	2	16
3	$PhMe_2SiH$	0	0	0	0	0
4	Et_3SiH	0	0	0	0	0
5	PHMS	21	3	0	1	6

[a]Reaction conditions: **1a** (0.1 mmol), HCO_2H (8.5 equiv.), Silane (10 equiv.), Catalyst (3 mol%), THF (2 mL), 18 h, 70ºC. [b] Determined by GC analysis using *n*-hexadecane as an internal standard.

Table SI2. Influence of the solvent on the catalytic *N*-methylation of **1a**.[a]



Entry	Solvent	Conversion [%][b]	Yield **2a** [%][b]	Yield **3a** [%][b]	Yield **4a** [%][b]	Yield **5a** [%][b]
1[c]	MeCN	50	10	1	5	4
2	MeOH	6	0	0	0	4
3[c]	Toluene	99	41	5	13	13
4	THF	>99	1	0	2	97

[a]Reaction conditions: **1a** (0.1 mmol), HCO_2H (8.5 equiv.), $PhSiH_3$ (10 equiv.), Catalyst (3 mol%), Solvent (2 mL), 18 h, 70ºC. [b] Determined by GC analysis using hexadecane as an internal standard. [c] The urea intermediate 1,3-dimethyl-1,3-di-*p*-tolylurea is detected by GC-Mass.

3. ESI mass spectra from the reaction mixture during the *N*-methylation of 1a.

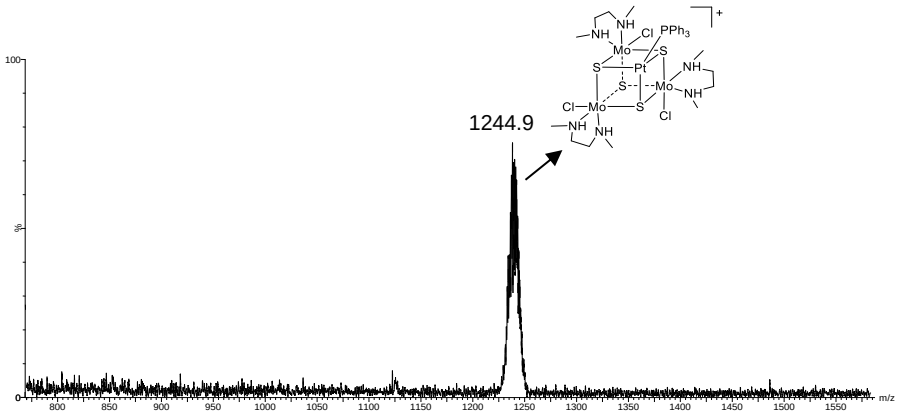


Figure SI5. ESI mass spectrum from the *N*-methylation reaction after 8 hours.

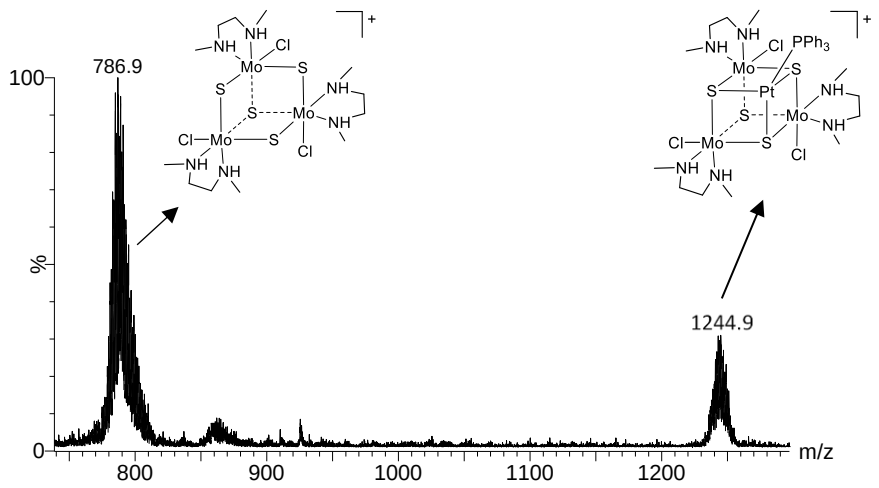
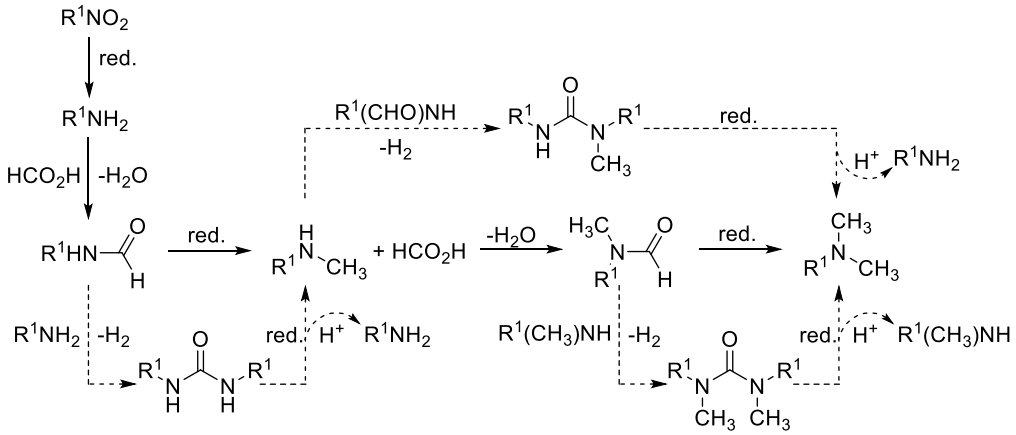


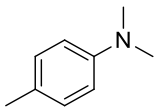
Figure SI6. ESI mass spectrum from the mixture of $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (**1**(BF4)) (0.003 mmol) and $Pt(PPh_3)_4$ **(2)** (0.001 mmol) in THF after 10 minutes stirring at room temperature.

4. Reaction pathway investigation.

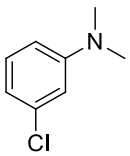


Scheme SI1. Proposed pathways for the direct *N*-methylation of nitroarenes with formic acid in the presence of the heterobimetallic $\mathbf{3}^{+}$ catalyst.

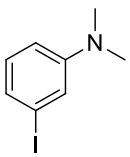
5. Characterization data of isolated products.



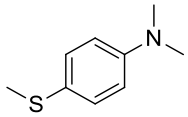
N,N,4-trimethylaniline:[1] ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.03 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 2.88 (s, 6H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 149.53, 130.00, 126.39, 113.56, 41.43, 20.48; MS (EI): m/z (rel. Int) 135.



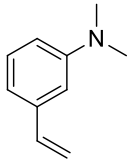
3- Chloro-N,N-dimethylaniline:[1] ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.13 (t, J = 8.1 Hz, 1H), 6.70 – 6.56 (m, 3H), 2.94 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 152.26, 135.31, 130.50, 116.33, 112.51, 111.04, 40.69; MS (EI): m/z (rel. Int) 155.



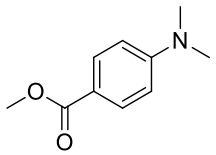
3-iodo-N,N-dimethylaniline:[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 – 7.02 (m, 2H), 6.96 – 6.91 (m, 1H), 6.69 – 6.65 (m, 1H), 2.93 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.68, 130.51, 125.33, 121.21, 111.70, 95.67, 40.45; MS (EI): m/z (rel. Int) 247.



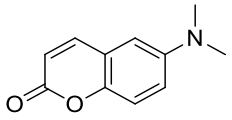
N,N-dimethyl-4-(methylthio)aniline: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.14 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 2.81 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 134.63, 131.47, 128.45, 113.83, 41.02, 19.24; MS (EI): *m*/*z* (rel. Int) 167.



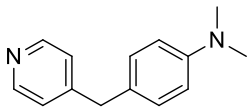
N,N-dimethyl-3-vinylaniline: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.23 (t, *J* = 7.6 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.77 – 6.65 (m, 2H), 5.78 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 3.00 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 151.61, 138.84, 138.39, 129.65, 115.06, 113.46, 112.88, 111.08, 40.94; MS (EI): *m*/*z* (rel. Int) 147.



Methyl 4-(dimethylamino)benzoate: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.76 (d, *J* = 9.1 Hz, 2H), 6.56 (d, *J* = 9.1 Hz, 2H), 3.72 (s, 3H), 2.92 (s, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 167.72, 153.99, 131.58, 117.44, 111.22, 51.79, 40.39; MS (EI): *m*/*z* (rel. Int) 179.



6-(dimethylamino)-2H-chromen-2-one: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.65 (d, *J* = 9.5 Hz, 1H), 7.20 (d, *J* = 9.1 Hz, 1H), 6.97 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.70 (d, *J* = 3.0 Hz, 1H), 6.32 (d, *J* = 9.5 Hz, 1H), 2.96 (s, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 161.52, 148.05, 146.58, 144.03, 119.58, 117.42, 117.22, 116.97, 109.50, 41.01; MS (EI): *m*/*z* (rel. Int) 189.

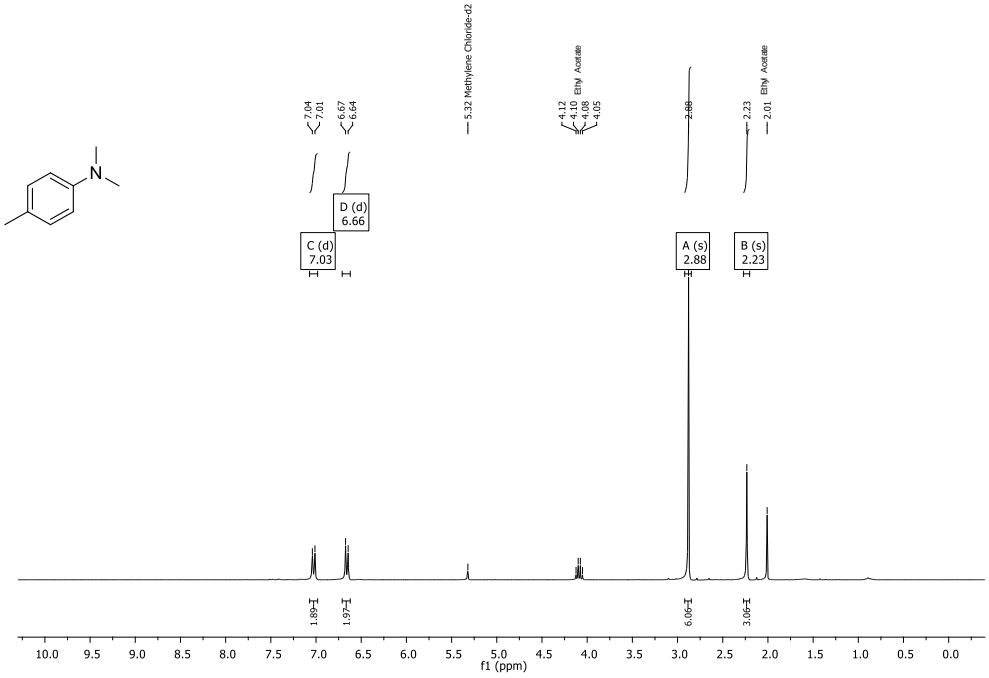


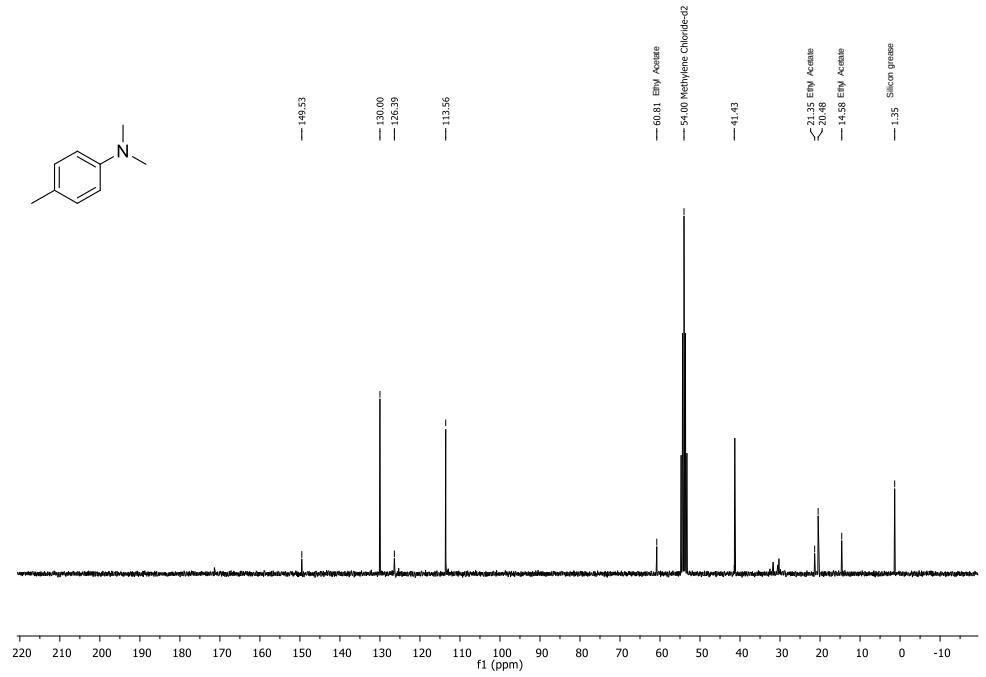
N,N-dimethyl-4-(pyridin-4-ylmethyl)aniline: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.41 – 8.36 (m, 2H), 7.08 – 7.02 (m, 4H), 6.73 – 6.66 (m, 2H), 3.85 (s, 2H), 2.92 (s, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 151.97, 149.95, 130.13, 128.27, 127.42, 124.59, 113.39, 41.02, 40.77; MS (EI): *m*/*z* (rel. Int) 212.

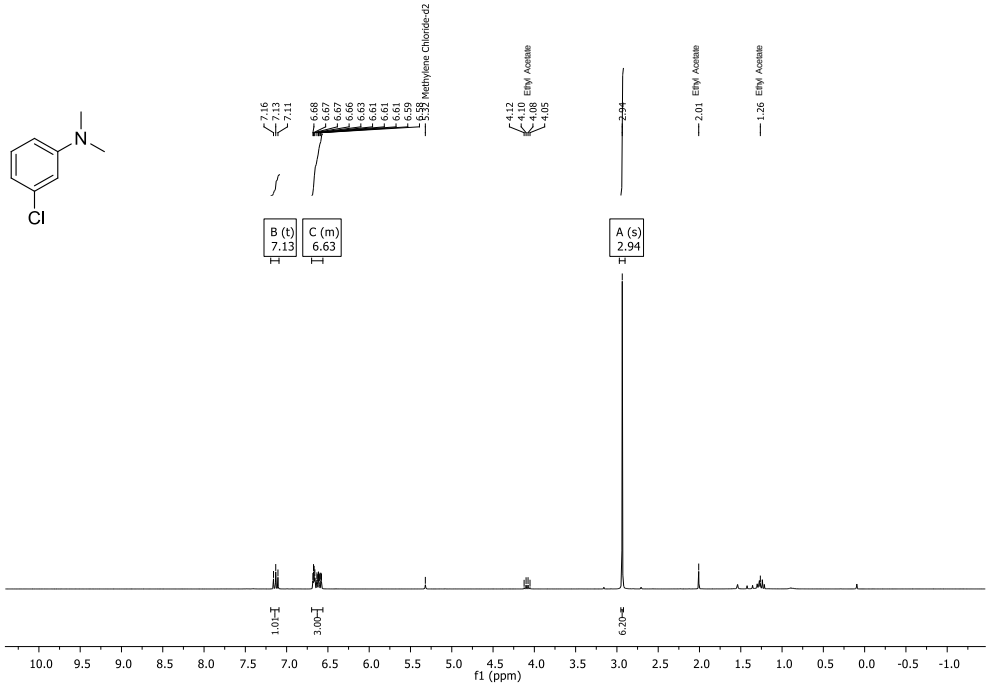
6. References.

[1] X. Jiang, C. Wang, Y. Wei, D. Xue, Z. Liu and J. Xiao, *Chem. Eur. J.* **2014**, *20*, 58–63.

7. ^{1}H NMR and ^{13}C NMR spectra of isolated products.



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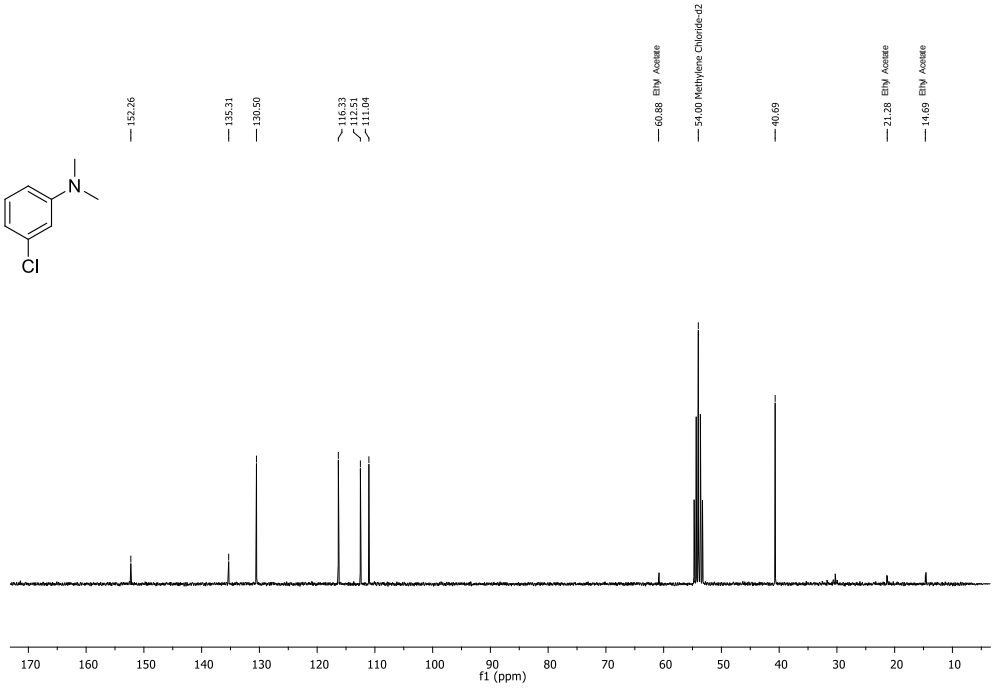
7.11
6.68
6.67
6.67
6.66
6.65
6.61
6.61
6.61
6.59
6.58
5.32 Methylene Chloride-d2
4.12
4.10
4.08
4.05 Ethyl Acetate
2.94
2.01 Ethyl Acetate
1.26 Ethyl Acetate
B (t)
7.13
C (m)
6.63
A (s)
2.94
1.01
3.00
6.20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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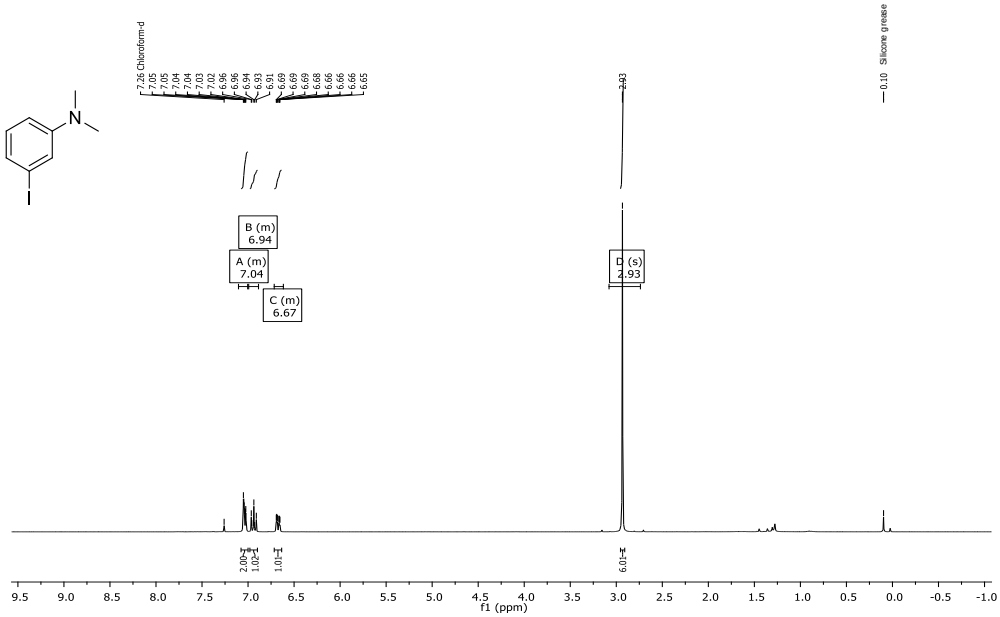
135.31
130.50
116.33
113.51
111.04
60.88 Ethyl Acetate
54.00 Methylene Chloride-d2
40.69
21.28 Ethyl Acetate
14.69 Ethyl Acetate
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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7.05
7.04
7.04
7.03
7.03
6.96
6.96
6.94
6.93
6.91
6.69
6.69
6.69
6.68
6.66
6.66
6.65
6.65
2.93
0.10 Silicone grease
B (m) 6.94
A (m) 7.04
C (m) 6.67
D (s) 2.93
2.00
1.02
1.01
6.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
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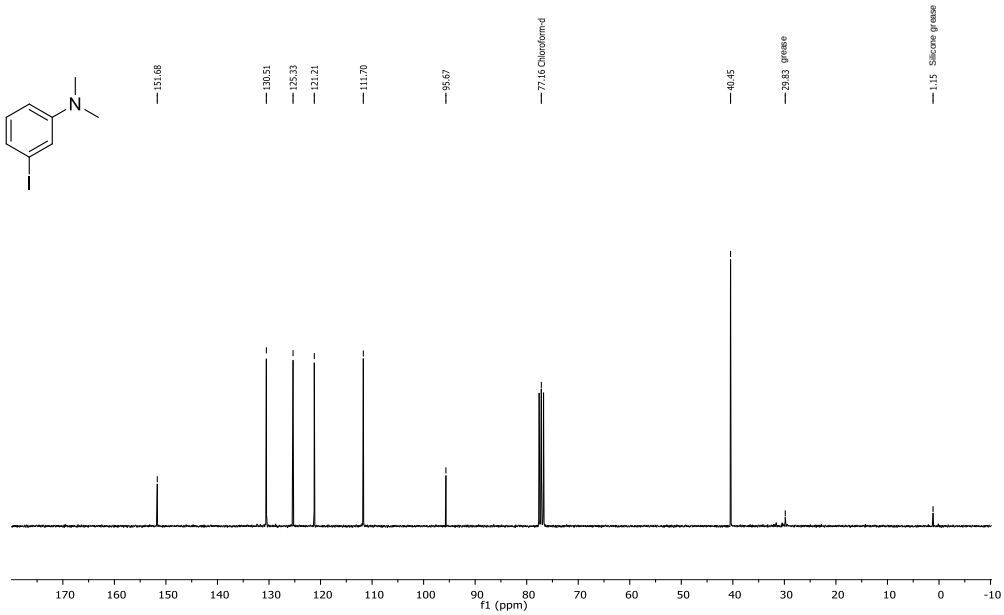
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130.51
125.33
121.21
111.70
95.67
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40.45
29.83 grease
1.15 Silicone grease
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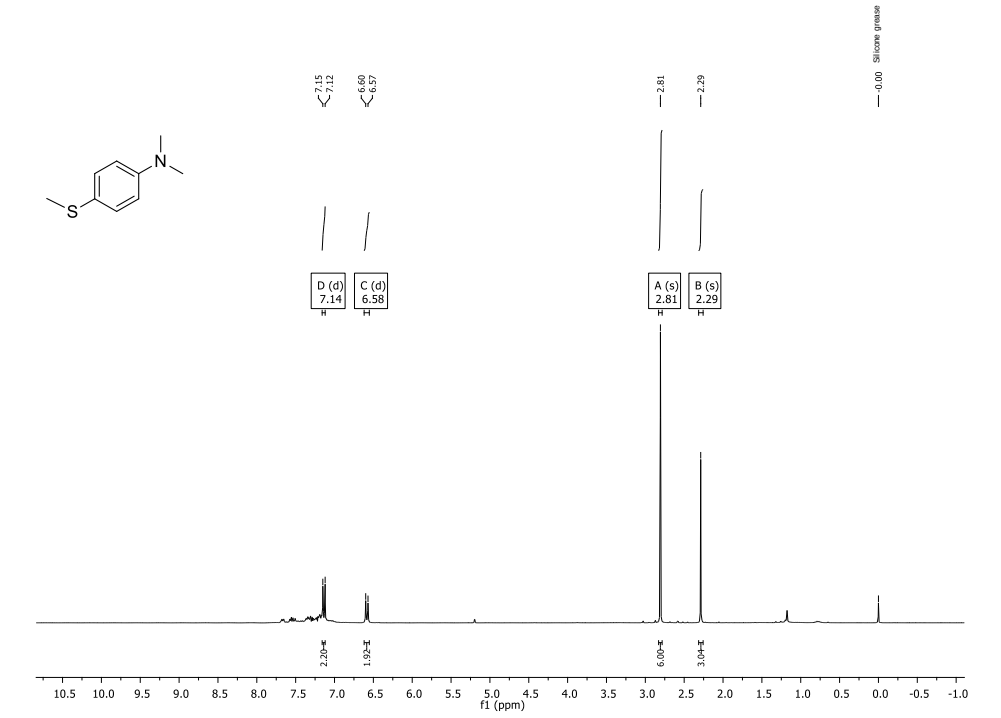
f1 (ppm)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2.29
-0.00
Silicone grease
D (d)
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A (s)
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B (s)
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1.92
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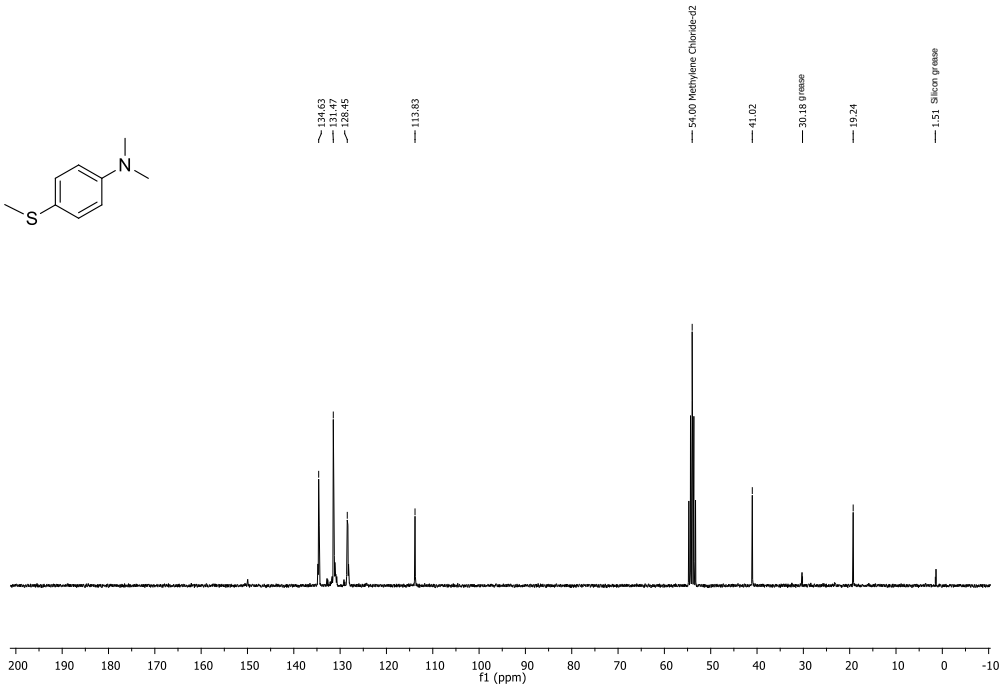
3.04
f1 (ppm)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113.83
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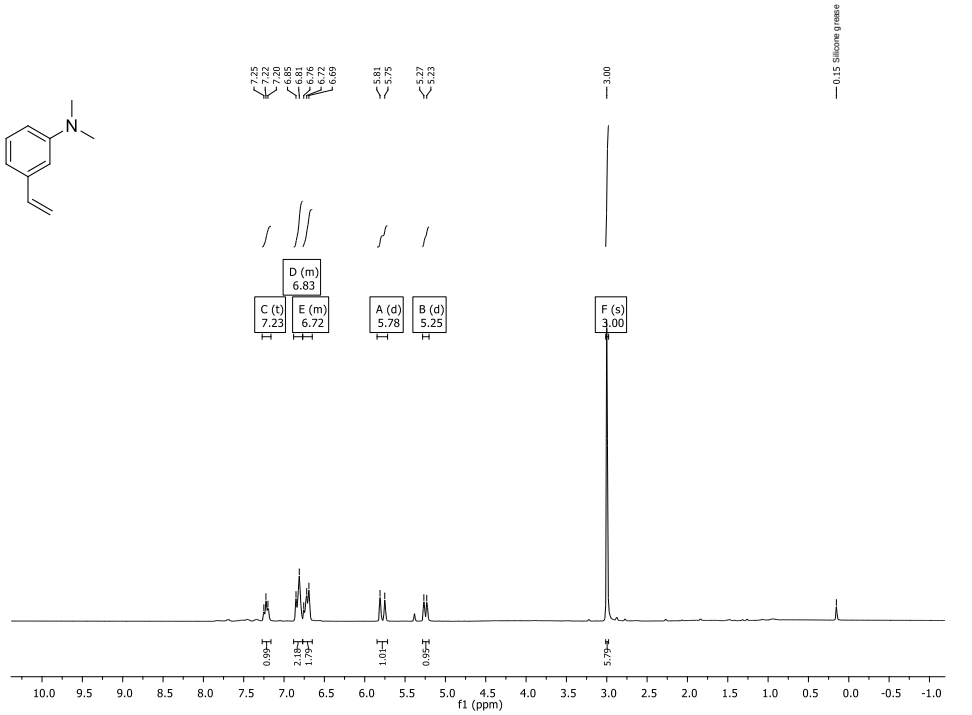
41.02
30.18 grease
19.24
1.51 Silicon grease
f1 (ppm)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7.22
7.20
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6.76
6.72
6.69
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5.27
5.23
3.00
0.15 Silicone grease
D (m)
6.83
C (t)
7.23
E (m)
6.72
A (d)
5.78
B (d)
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F (s)
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1.01
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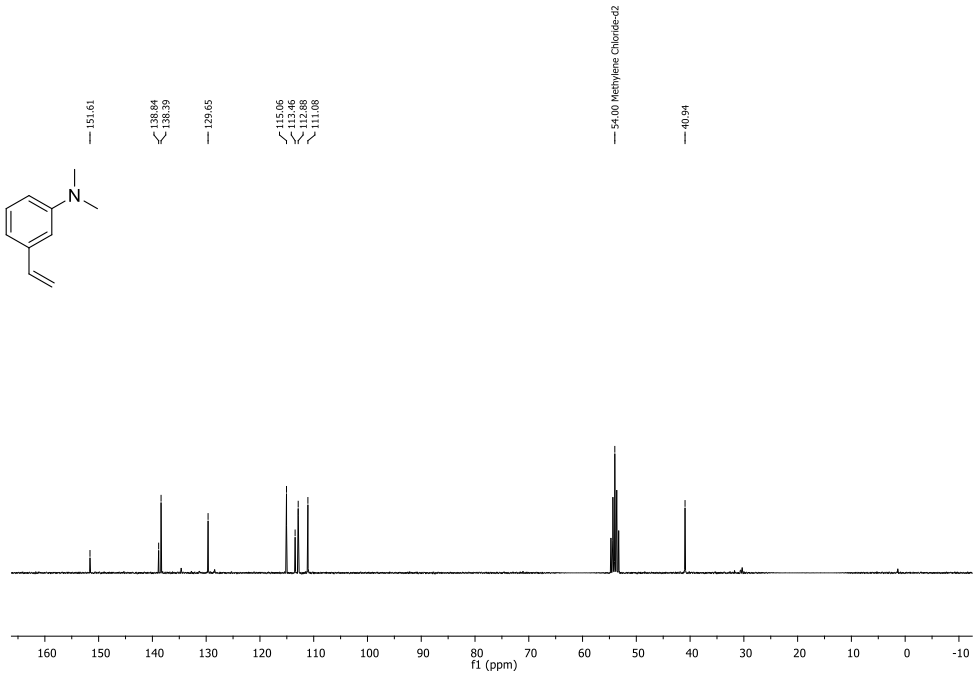
5.79
f1 (ppm)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138.84
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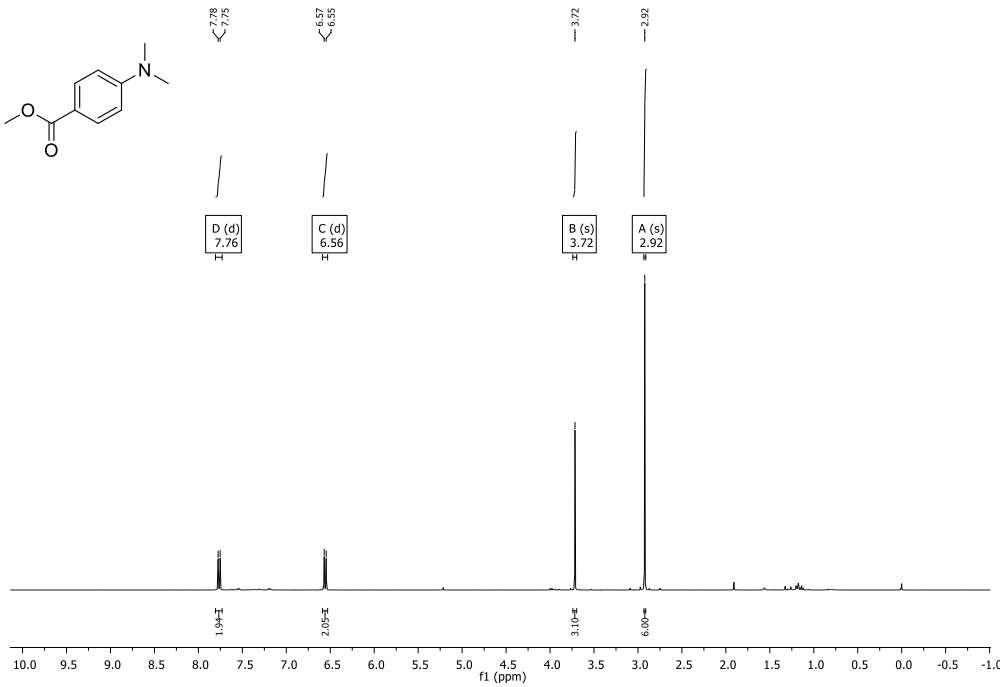
129.65
115.06
113.46
112.88
111.08
54.00 Methylene Chloride-d2
40.94
f1 (ppm)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2.92
D (d)
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C (d)
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B (s)
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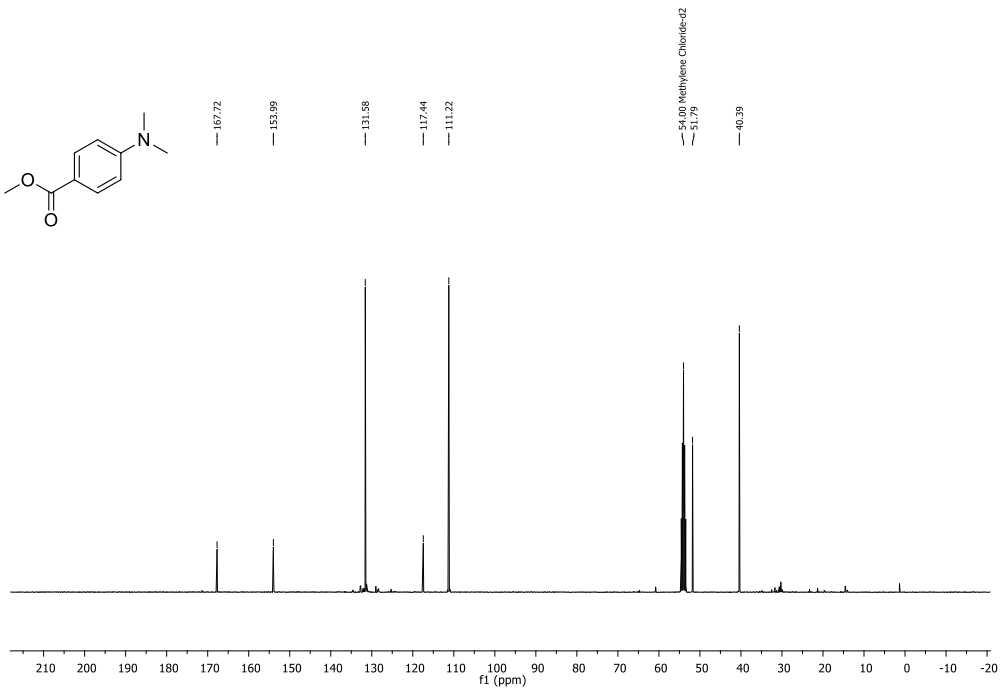
6.00
f1 (ppm)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40.39
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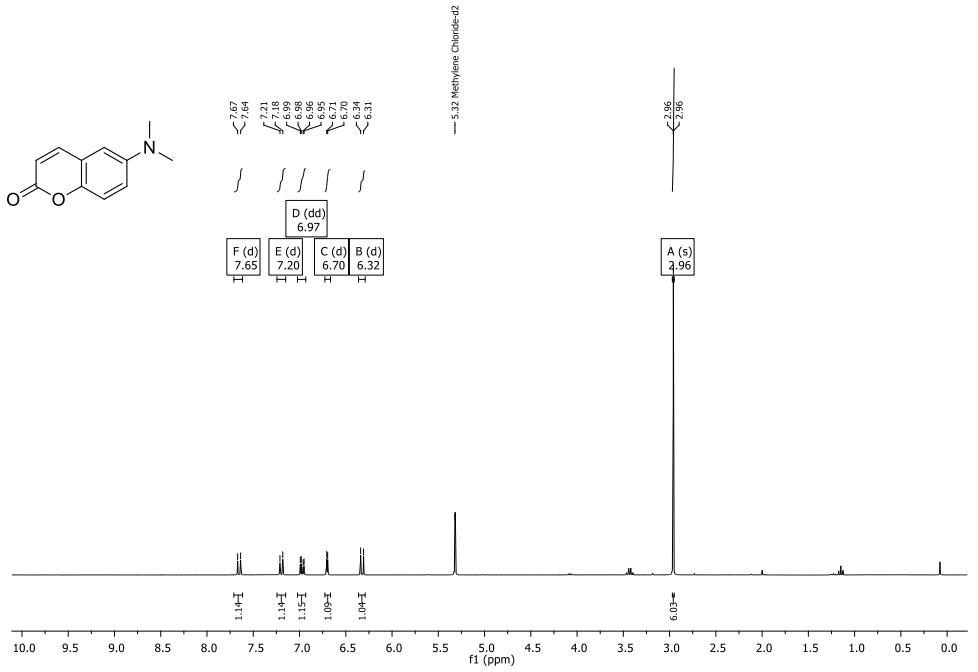
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2.96
2.96
D (dd)
6.97
F (d)
7.65
E (d)
7.20
C (d)
6.70
B (d)
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A (s)
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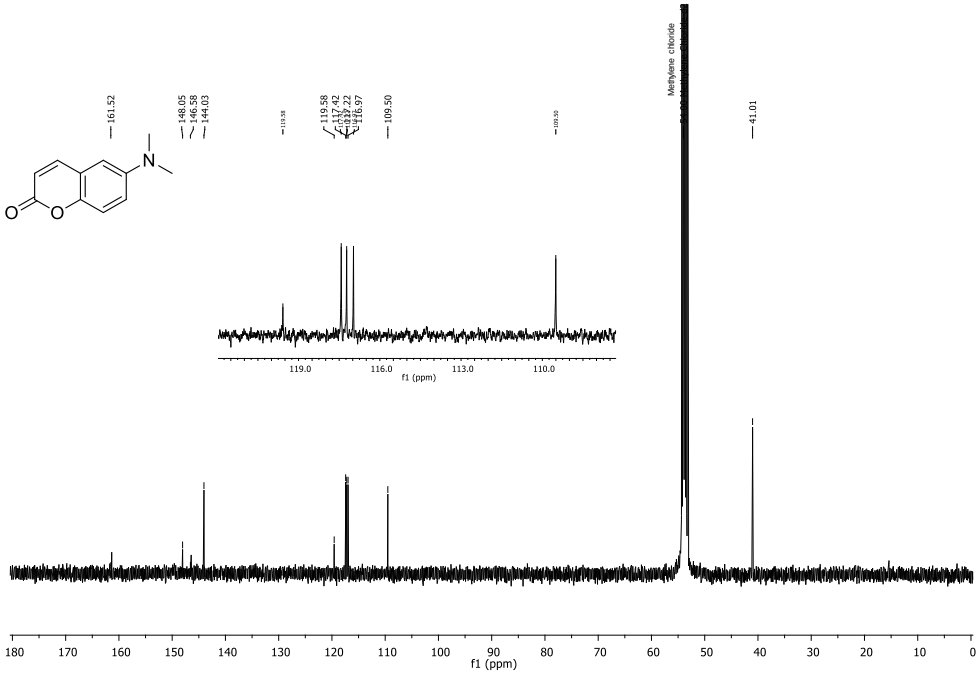
6.03
f1 (ppm)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119.58
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117.22
116.97
109.50
Methylene chloride
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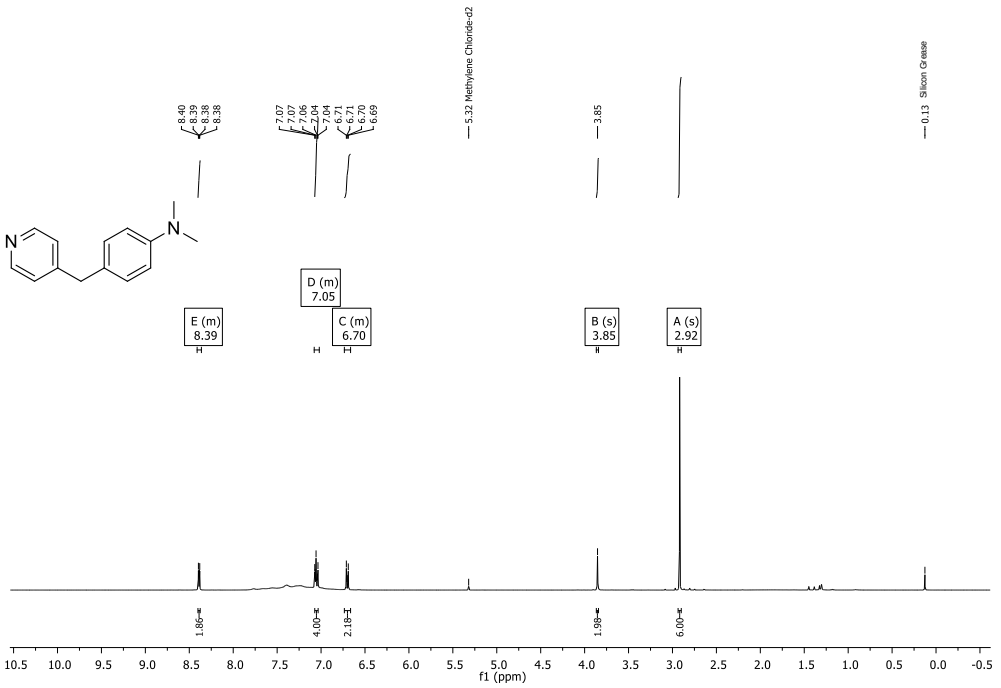
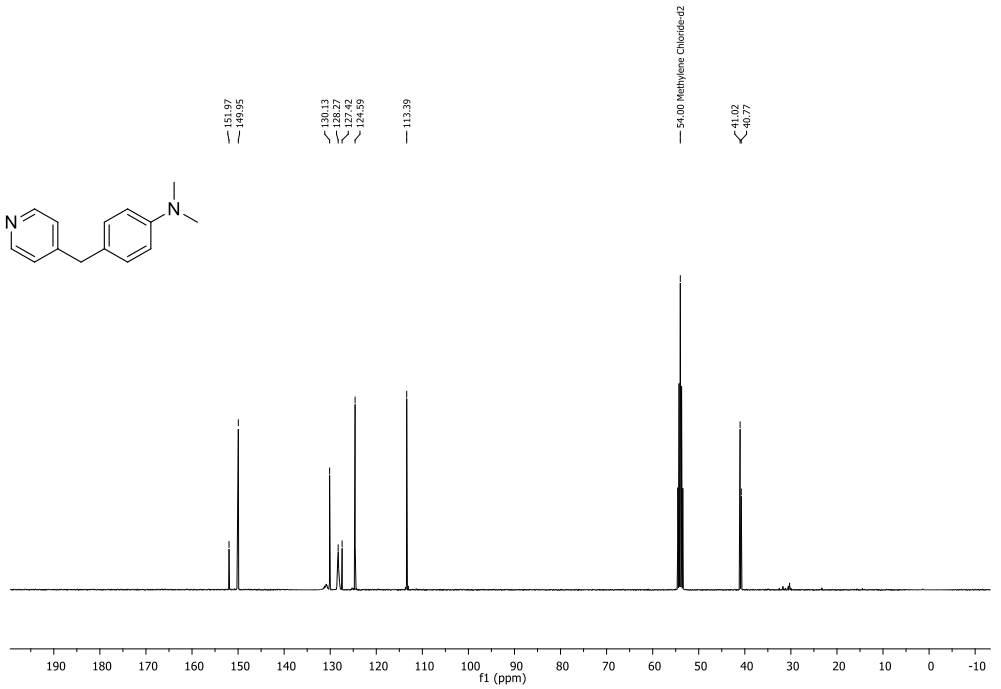
119.0
116.0
113.0
110.0
f1 (ppm)
f1 (ppm)


8.40
8.39
8.38
8.38
7.07
7.07
7.06
7.04
7.04
6.71
6.71
6.70
6.69
5.32 Methylene Chloride-d2
3.85
0.13 Silicon Grease
N
N
D (m)
7.05
E (m)
8.39
C (m)
6.70
B (s)
3.85
A (s)
2.92
1.86
4.00
2.18
1.98
6.00
f1 (ppm)


151.97
149.95
130.13
128.27
127.42
124.59
113.39
54.00 Methylene Chloride-d2
41.02
40.77
N
N
f1 (ppm)

7

Discusión general de los resultados

7. Discusión general de los resultados
   - 7.1. Antecedentes
   - 7.2. Síntesis y caracterización de los clústeres Mo_3S_4 y Mo_3PtS_4
   - 7.3. Aplicaciones catalíticas de los clústeres Mo_3S_4 y Mo_3PtS_4

"La ciencia es todo aquello sobre lo cual siempre cabe discusión."

José Ortega y Gasset

7.1. Antecedentes

Las aminas son productos orgánicos utilizados frecuentemente a escala de laboratorio y en la industria. Entre sus usos más comunes cabe destacar su utilización en la preparación de pigmentos, productos químicos para la agricultura y medicamentos.[1,2] De hecho, dada su participación en la regulación de procesos biológicos, alrededor de 35 de los 50 medicamentos más utilizados en el año 2014 contenían grupos nitrógeno y/o amino en su composición.[3–6]

La principal vía de síntesis de aminas aromáticas funcionalizadas es la reducción selectiva de nitroarenos. Tradicionalmente en la industria, dicha reducción se hace utilizando métodos estequiométricos que, desde un punto de vista medioambiental, son caros e insostenibles por la gran cantidad de residuos que generan. Por este motivo, algunos de estos métodos se están sustituyendo por protocolos catalíticos, en su mayoría en fase heterogénea.[7] Tal como se ha comentado en el capítulo de introducción de esta tesis, la catálisis heterogénea presenta como ventaja fundamental la reutilización del catalizador. En contrapartida, los catalizadores homogéneos resultan ser mucho más selectivos, ya que con ellos se alcanza un mayor control de la reactividad. La reducción catalítica de nitroarenos utiliza, por lo general, metales nobles como catalizadores con una tendencia cada vez mayor hacia el uso de nanopartículas metálicas.[8–13] Actualmente, se está realizando un esfuerzo considerable dirigido a sustituir estos metales nobles por otros más económicos y menos contaminantes que contribuyan al diseño de procesos químicos sostenibles. Como consecuencia, los últimos años han sido testigo de un desarrollo de sistemas heterogéneos y homogéneos que utilizan catalizadores basados en metales como hierro, cobalto o molibdeno.[14–24]

Existen diversas estrategias para llevar a cabo la reducción de nitroarenos, de entre las cuales la hidrogenación catalítica ha experimentado un progreso significativo. El hidrógeno molecular es la fuente reductora más limpia y respetuosa

con el medioambiente, ya que el agua es el único subproducto que se genera. Sin embargo, la necesidad de utilizar sistemas especiales y el peligro que implica la manipulación de este gas, han impulsado la utilización de agentes reductores alternativos. Diversas fuentes de hidrógeno tales como silanos, ácidos, acoholes, boranos o hidracina, ofrecen la posibilidad de llevar a cabo la reducción de nitroarenos sin la necesidad de trabajar a presión y, en algunos casos, en condiciones de reacción relativamente suaves. Esta circunstancia ha propiciado el uso de estos reactivos a pesar de que el exceso requerido para la transformación catalítica genera productos secundarios. La eliminación de dichos productos precisa de tratamientos posteriores cuya dificultad depende de la naturaleza del agente reductor utilizado.

Nuestro trabajo se ha centrado en la utilización de sulfuros de molibdeno como catalizadores alternativos a los metales nobles, que son caros y, en algunos casos, tóxicos. Al inicio de esta tesis doctoral, existían pocos sistemas en los que se utilizaran catalizadores basados en sulfuros de molibdeno para la reducción de nitrocompuestos. El primer antecedente en el ámbito de la catálisis heterogénea data de 1993 y utiliza MoS_2 como catalizador e hidrógeno a presiones moderadas (20 bar) como agente reductor. Este proceso consigue conversiones de nitrobenceno del orden del 30% trabajando a 130 ºC.[14] Posteriormente, Chen y colaboradores siguen el mismo protocolo pero utilizan un catalizador de MoS_2 intercalado con zirconio sin que se observe una mejora apreciable en la conversión.[15] Sin embargo, ninguno de estos trabajos aborda el tema de la selectividad. En 2013, Huang y colaboradores consiguen reducir un número limitado de derivados de nitrobenceno a anilinas en presencia de MoS_2 a 60 ºC, pero utilizan hidracina como agente reductor, un compuesto muy tóxico.[25] La modificación de este disulfuro de molibdeno con oxígeno supone una mejora de la quimioselectividad cuando el nitrobenceno se halla funcionalizado con grupos fácilmente reducibles tales como C=C, C≡C ó C≡N.[26] Corma y colaboradores han preparado, este mismo año, un material de MoS_2 nanoestructurado dopado con cobalto capaz de reducir de manera selectiva un

amplio abanico de nitroarenos bajo presiones moderadas de hidrógeno (11 bar) y 150 ºC de temperatura.[20]

Tal como se ha mencionado anteriormente, la catálisis homogénea conduce, por lo general, a procesos catalíticos de mayor selectividad. En el capítulo de introducción de esta tesis, se han destacado los clústeres $[MeCpMo(\mu\text{-}S)]_2S_2CH_2$ y $[MeCpMo(\mu\text{-}S)(\mu\text{-}SH)]_2$ desarrollados por Dubois y colaboradores y su capacidad para reducir el nitrobenceno a anilina con hidrógeno molecular bajo condiciones suaves de presión y temperatura. En este estudio, publicado en los años ochenta, los autores no evalúan la selectividad del catalizador.[27] La unidad trinuclear $Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3$ de los clústeres estudiados en esta tesis doctoral guarda similitud, tanto electrónica como estructural, con estos clústeres dinucleares, ya que los átomos de molibdeno se encuentran también en un estado de oxidación (IV) y están unidos por azufres puente. Los clústeres Mo_3S_4 de fórmula $[Mo_3S_4H_3(dmpe)_3]^+$ (dmpe = 1,2-(bis)dimetilfosfinoetano) y $[Mo_3S_4Cl_3(edpp)_3]^+$ (edpp = 2-(aminoetil)difenilfosfina), representados en la Figura 1, catalizan la reducción quimioselectiva de nitroarenos a anilinas mediante un mecanismo de transferencia de hidrógeno. La reacción tiene lugar a 80 ºC utilizando una mezcla de ácido fórmico y trietilamina como fuente reductora. Estos clústeres funcionalizados con difosfinas o aminofosfinas también presentan una actividad moderada en presencia de silanos, pero no son activos cuando se utiliza hidrógeno molecular como agente reductor.

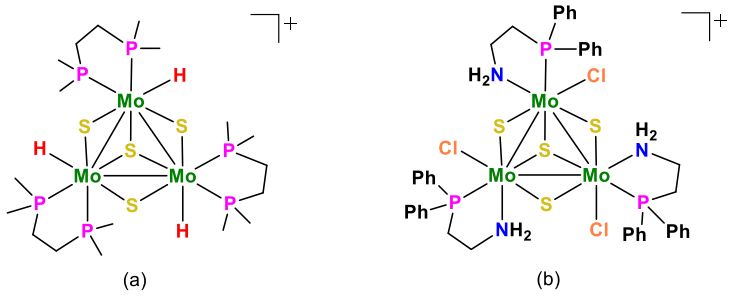


Figura 1. Estructuras de los clústeres $[Mo_3S_4H_3(dmpe)_3]^+$ (a) y $[Mo_3S_4Cl_3(edpp)_3]^+$ (b).

El potencial de los clústeres Mo_3S_4 como catalizadores en la reducción de nitroarenos se describe por primera vez en 2012 por el grupo donde se ha realizado la presente tesis doctoral en colaboración con el Profesor Matthias Beller.[28] Además de abordar la quimioselectividad del proceso, en dicho trabajo se consigue identificar mediante técnicas de caracterización *in situ* el complejo hidruro $[Mo_3S_4H_3(dmpe)_3]^+$ como la especie catalíticamente activa. La monitorización del proceso se lleva a cabo mediante la técnica denominada *PSI* (*Pressurized Sample Infusion*) en combinación con espectrometría de masas. Dicho estudio apoya la propuesta de ciclo catalítico representado en la Figura 2.

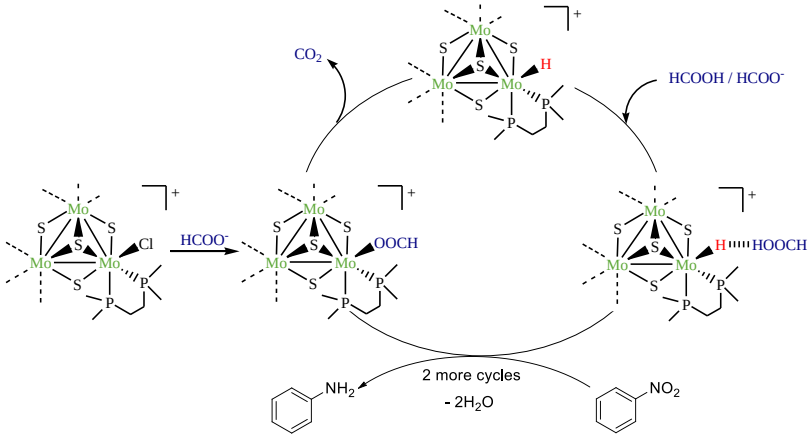


Figura 2. Ciclo catalítico para las especies clúster involucradas en la reducción de nitrobenceno a anilina.

De acuerdo con este ciclo, las especies de dihidrógeno que se generan al añadir ácido a la especie hidruro transfieren el átomo de hidrógeno al nitroareno con la consiguiente formación de la anilina tras sucesivos ciclos de reacción. Posteriormente, el clúster hidruro se regenera a partir del complejo formiato $[Mo_3S_4(HCOO)_3(dmpe)_3]^+$ mediante un proceso de β-eliminación. Alternativamente, la especie activa también puede generarse *in situ* a partir del haluro

$[Mo_3S_4Cl_3(dmpe)_3]^+$ mediante la reacción con ácido fórmico en medio básico, tal como se observa en el ciclo.

En el caso de la reducción catalítica de nitroarenos con clústeres funcionalizados con aminofosfinas, el protocolo se lleva a cabo a partir de los clústeres haluro que actúan como precatalizadores dada la imposibilidad de aislar los hidruros correspondientes.[29] En este caso, la monitorización de la reacción muestra la coexistencia de varias especies durante el proceso catalítico, lo que dificulta la identificación de la especie activa y por tanto la elucidación del ciclo catalítico.

Con estos antecedentes, y motivados por la presencia de ligandos amino en gran variedad de catalizadores de procesos de reducción, decidimos extender la química de los sulfuros clúster de molibdeno a la coordinación de ligandos de dicha naturaleza y ver de qué manera afectaba esta sustitución a la reactividad de los clústeres de unidad Mo_3S_4.[30] Tras la síntesis y caracterización de los nuevos clústeres diamino, esta tesis se ha centrado en la búsqueda de aplicaciones catalíticas de dichos complejos dirigidas a la obtención de aminas, dada la importancia de éstas en la industria.

7.2. Síntesis y caracterización de los clústeres Mo_3S_4 y Mo_3PtS_4

La robustez de la unidad Mo_3S_4 permite obtener de manera sencilla un gran número de derivados mediante reacciones de sustitución de ligandos, tal y como se enfatiza en el capítulo 1.[31] Esta particularidad contrasta con el limitado número de clústeres Mo_3S_4 que contienen ligandos amina ocupando sus posiciones de coordinación externas. La funcionalización de la unidad trinuclear con aminas ocurre, preferentemente, cuando estos ligandos actúan como tridentados, tales como los derivados del triazaciclononano (tacn) y de la dietilentriamina (dien), representados en la Figura 3.[32,33]

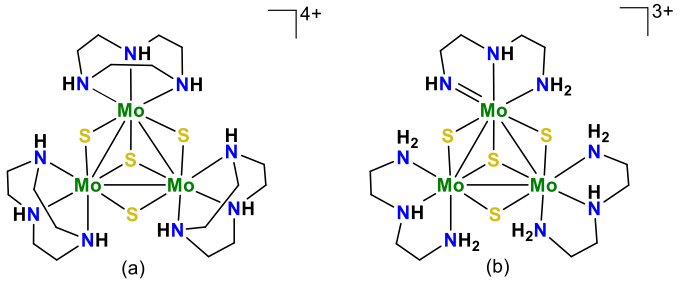


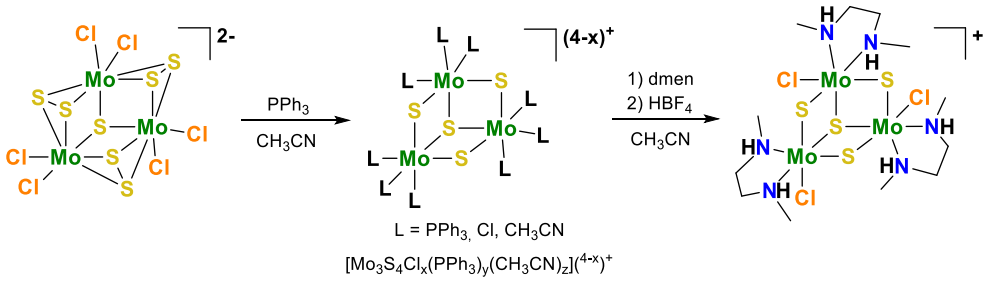
Figura 3. Clústeres Mo_3S_4 funcionalizados con ligandos triamina.

Los clústeres $[Mo_3S_4(tacn)_3]^{4+}$ (Figura 3a) y $[Mo_3S_4(dien^-)(dien)_2]^{3+}$ (Figura 3b) se obtienen con rendimientos de alrededor del 60% al sustituir las moléculas de agua del clúster $[Mo_3S_4(H_2O)_9]^{4+}$ por los ligandos tridentados. Dado que el clúster acuo precursor es estable únicamente en condiciones ácidas, la protonación de los ligandos amina supone una reacción competitiva que dificulta la obtención de estos clústeres en elevados rendimientos y es necesario un gran control del pH y de la temperatura. En el caso del clúster $[Mo_3S_4(dien^-)(dien)_2]^{3+}$, representado en la Figura 3b, el análisis cristalográfico muestra que uno de los enlaces Mo-N es de orden dos (1.987 Å) y que, por tanto, la desprotonación de uno de los nitrógenos conduce a la formación de especies insaturadas metal-imino.

Hegetschweiler y colaboradores han preparado clústeres Mo_3S_4 funcionalizados con ligandos amina multidentados que combinan la coordinación a través de los átomos de nitrógeno con la de los de oxígeno, como es el caso de los complejos $[Mo_3S_4(taci)_3]^{4+}$ (taci = 1,3,5-triamino-1,3,5-trideoxi-*cis*-inositol) y $[Mo_3S_4(tdci)_3]^{4+}$ (tdci = 1,3,5-trideoxi-1,3,5-tris(dimetilamino)-*cis*-inositol).[34,35] Para la síntesis de estos clústeres catiónicos, los autores hacen reaccionar un precursor de unidad Mo_3S_4, el cual se prepara *in situ* a partir del complejo $(NEt_4)_2[Mo_3S_7Br_6]$ y trifenilfosfina, con los ligandos taci y tdci en etanol a reflujo. Finalmente, los compuestos se aíslan como unos cristales verdes con un 30 % de rendimiento para el complejo con ligandos taci y un 75 % para el clúster análogo funcionalizado con tdci.

Las diferencias en los rendimientos se deben a la presencia de reacciones competitivas consecuencia de los distintos modos de coordinación que ofrecen estos ligandos.

La generación *in situ* de la especie Mo_3S_4 por tratamiento con trifenilfosfina del precursor $[Mo_3S_7X_6]^{2-}$ (X = Cl o Br), se ha utilizado también con éxito para la síntesis de clústeres funcionalizados con difosfinas electroactivas o solubles en agua.[36–38] En este trabajo, se ha seguido esta estrategia de síntesis para la obtención del clúster $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ (dmen = *N,N'*-dimetiletilendiamina). El Esquema 1, resume la secuencia de reacciones llevadas a cabo para la preparación del clúster funcionalizado con dicha diamina en rendimientos del 75%.[39]



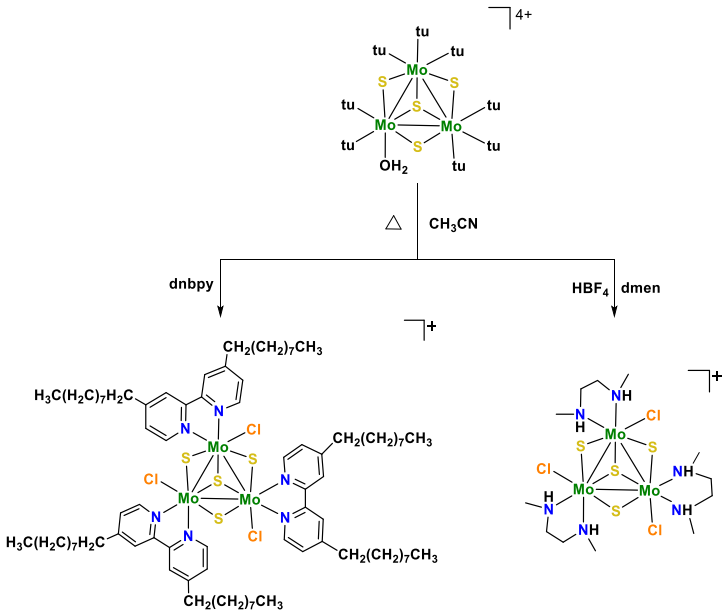
Esquema 1. Ruta sintética para la obtención del clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ a paritr del ion $[Mo_3S_7Cl_6]^{2-}$.

La adición de una pequeña cantidad de ácido es necesaria para evitar la sustitución de algunos ligandos cloruro por ligandos hidroxilo, los cuales se generan a partir de las trazas de agua presentes en el medio de reacción. Cabe destacar que, durante el proceso de síntesis, se forma exclusivamente uno de todos los posibles isómeros, donde el halógeno ocupa la posición *trans* al azufre puente, tal y como ocurre en los clústeres análogos difosfino y aminofosfino.[40,41] El nuevo complejo es soluble en disolventes orgánicos comunes tales como acetonitrilo, diclorometano o tetrahidrofurano y, además, es altamente soluble en agua y en alcoholes como metanol o etanol. El principal inconveniente de esta ruta sintética radica en la dificultad de eliminar tanto el exceso de trifenilfosfina como las sales de

tetrabutilamonio procedentes del precursor $(nBu_4N)_2[Mo_3S_7Cl_6]$, hecho que nos ha llevado a buscar rutas alternativas.

La solubilidad en agua del complejo $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ hizo pensar en el clúster acuo $[Mo_3S_4(H_2O)]^{4+}$ como precursor. Sin embargo, las condiciones de acidez necesarias para garantizar su estabilidad resultan incompatibles con la presencia de aminas ante la posibilidad de protonación de las mismas. Por lo tanto, esta vía de síntesis quedó descartada y decidimos buscar otras opciones. En colaboración con el Instituto Nikolaev de Novosibirsk, hemos desarrollado un proceso que sustituye los ligandos acuo por ligandos tiourea para obtener el complejo $[Mo_3S_4(tu)_8(H_2O)]^{4+}$.[42] Además de no necesitar un pH ácido, la elevada labilidad de los ligandos tiourea convierte a este clúster en un precursor ideal para la funcionalización de la unidad Mo_3S_4. Tanto es así que, en esta tesis, dicho precursor ha sido elegido para la obtención de clústeres diamino y diimino, según la ruta sintética representada en el Esquema 2. Tras su purificación, se obtienen los compuestos $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ y $[Mo_3S_4Cl_3(dnbpy)_3](PF_6)$ en rendimientos del 77% y del 80%, respectivamente.[43] Cabe resaltar, que la preparación del derivado diimino realizada en colaboración con el Instituto Nikolaev de Novosibirsk, no precisa de ácido para evitar la sustitución de los halógenos por grupos hidroxilo.

Los nuevos clústeres $[Mo_3S_4Cl_3(dmen)_3]^+$ y $[Mo_3S_4Cl_3(dnbpy)_3]^+$ se han caracterizado mediante espectrometría de masas, espectroscopía de resonancia magnética nuclear, análisis elemental y, en el caso del clúster diamino, por difracción de rayos X en monocristal. La presencia de las cadenas dinonilo en el clúster $[Mo_3S_4Cl_3(dnbpy)_3]^+$ ha hecho imposible la obtención de cristales susceptibles de ser medidos mediante difracción de rayos X.



Esquema 2. Ruta sintética para la obtención de los clústeres $[Mo_3S_4Cl_3(dmen)_3]^+$ y $[Mo_3S_4Cl_3(dnbpy)_3]^+$ a paritr del precursor $[Mo_3S_4(tu)_8(H_2O)]^{4+}$.

Los cristales del clúster diamino se obtuvieron por evaporación lenta de una disolución 1:1 de diclorometano y dietil éter. El complejo $[Mo_3S_4Cl_3(dmen)_3](BF_4)$ cristaliza en el grupo espacial *Pccn* y en la Figura 4 se muestra una representación ORTEP de su estructura.

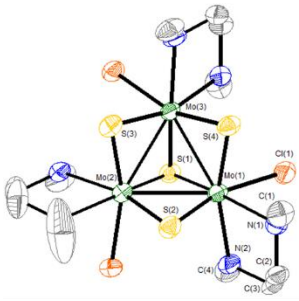


Figura 4. Representación ORTEP del clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ (elipsoides al 50% de probabilidad).

La estructura consiste en un cubo incompleto con simetría C_3 en el que los átomos de molibdeno y azufre ocupan los vértices adyacentes con una posición metálica vacante. Cada átomo de molibdeno presenta un entorno de coordinación octaédrico, sin tener en cuenta los enlaces metal-metal, con tres átomos de azufre, uno de cloro y dos de nitrógeno. El ligando diamina se coordina de manera asimétrica a la unidad trimetálica con un átomo de nitrógeno en posición *trans* al azufre apuntado (μ_3-S) y el otro en posición *cis*, lo que resulta en un clúster con quiralidad intrínseca. Sin embargo, debido a la ausencia de fuentes de quiralidad en el medio, el clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ se obtiene como mezcla racémica.[44–46]

Con fines comparativos, las principales distancias del clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ se listan en la Tabla 1 junto con las de algunos derivados estrechamente relacionados. Las distancias Mo-Mo en el clúster diamino son similares a las observadas en los complejos análogos funcionalizados con difosfinas, aminofosfinas o triaminas, y son acordes con un estado de oxidación IV del metal. Asimismo, las distancias Mo-(μ_3-S) son mayores que las Mo-(μ-S), de acuerdo con la tendencia general. Por otro lado, la disimetría observada en el clúster difosfino entre la distancia Mo-(μ-S) *trans* al enlace metal-fósforo y la Mo-(μ-S) *trans* al enlace metal-cloro es menos acusada en el clúster diamino, lo que se asocia a la similitud del efecto *trans* de los átomos de cloro y de nitrógneo. Las distancias Mo-N son equiparables a las que presenta el clúster triamino y son consistentes con un enlace sencillo entre los átomos, por lo que se descarta la desprotonación de los átomos de nitrógeno.

Tabla 1. Selección de distancias de enlace promedio para los compuestos $[Mo_3S_4Cl_3(dmen)_3]^+$, $[Mo_3S_4Cl_3(tacn)_3]^{4+}$, $[Mo_3S_4Cl_3(edpp)_3]^+$ y $[Mo_3S_4Cl_3(dmpe_3)]^+$.

Distancia (Å)	$[Mo_3S_4Cl_3(dmen)_3]^+$	$[Mo_3S_4Cl_3(tacn)_3]^{4+}$[a]	$[Mo_3S_4Cl_3(edpp)_3]^+$[b]	$[Mo_3S_4Cl_3(dmpe)_3]^+$[c]
Mo-Mo	2.759[3]	2.773[1]	2.7463[7]	2.766(4)
Mo-(μ_3-S)	2.335[4]	2.361[1]	2.3611[13]	2.360(9)
Mo-(μ-S)[d]	2.288[7]	-	2.2960[12]	2.290(7)
Mo-(μ-S)[e]	2.301[5]	2.278[1]	2.2863[12]	2.336(7)
Mo-N/P[f]	2.278[6]	2.23[0]	2.5414[14]	2.534(8)
Mo-N/P[g]	2.298[18]	2.29[0]	2.2733[4]	2.605(8)
Mo-Cl	2.492[14]	-	2.4625[15]	2.473(7)

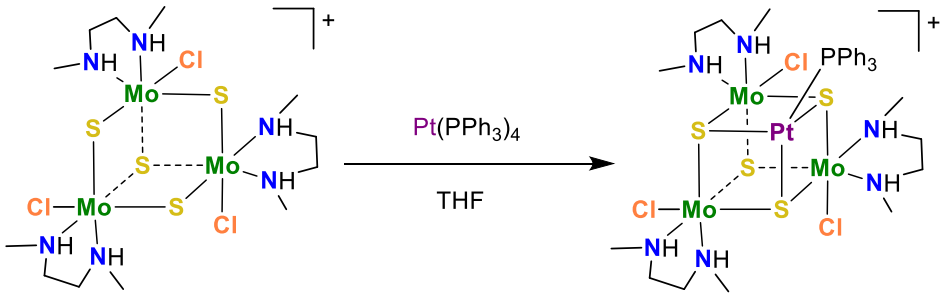
[a]Datos extraídos de la referencia [32]. [b]Datos extraídos de la referencia [41]. [c]Datos extraídos de la referencia [47]. [d]Distancia *trans* al enlace Mo-Cl. [e]Distancia *trans* al enlace Mo-N (Mo-P para el clúster funcionalizado con difosfinas). [f]Distancia *trans* al enlace Mo-(μ_3-S). [g]Distancia *cis* al enlace Mo-(μ_3-S). ( ) Desviación estándar de la medida. [ ] Desviación estándar del promedio.

Desde el punto de vista de la Química de Coordinación, los clústeres trinucleares Mo_3S_4 actúan como metaloligandos tridentados frente a un segundo metal de naturaleza variada, lo que ha permitido obtener a lo largo de los años una gran variedad de clústeres $Mo_3M'S_4$ tanto en medio acuoso como orgánico.[31,48–50] Como se ha comentado en el capítulo de introducción, el primer ejemplo de inserción de un heterometal en la posición vacante de un clúster Mo_3S_4 data de 1986, y lo describen Shibahara y colaboradores para la obtención del clúster de fórmula $[Mo_3Fe(H_2O)S_4(H_2O)_9]^{4+}$ a partir del complejo acuo $[Mo_3S_4(H_2O)_9]^{4+}$.[51] El precursor más común para la síntesis de complejos con unidad $Mo_3M'S_4$ es el ion acuo, al cual se han incorporado tanto metales de transición como de post-transición. Posteriormente, esta estrategia de construcción por bloques se ha extendido a los clústeres de fórmula $[Mo_3S_4(\eta^5\text{-}Cp^{\#})_3]^+$ ($Cp^{\#}$ = C_5H_5, C_5H_4Me o C_5Me_5) o a los complejos funcionalizados con difosfinas $[Mo_3S_4X_3(difosfina)_3]^+$ (X = halógenos). En este último caso, se han aislado los clústeres heterobimetálicos con metales de la primera serie de transición como hierro, cobre, cobalto y níquel, así como el clúster con platino $[Mo_3Pt(CO)S_4Cl_3(dmpe)_3]^+$ que constituye el primer derivado difosfino al que se ha incorporado un metal de la tercera serie de transición.[48,52–54]

Si bien existe una gran variedad de clústeres $Mo_3M'S_4$, el número de complejos que incorporan platino es limitado. El primero de ellos fue publicado por Hidai y colaboradores en el año 2000 quienes, tras hacer reaccionar el precursor $[Mo_3S_4(H_2O)_9]^{4+}$ con el complejo de platino (0) $[Pt(dba)_2]$ (dba = 1,5-difenil-1,4-pentadien-3-ona) en metanol, obtienen un intermedio que no son capaces de caracterizar, pero que formulan de manera tentativa como $[Mo_3Pt(dba)S_4(H_2O)_9]^{4+}$. El tratamiento de una disolución de dicho complejo tetranuclear con 3 equivalentes de dppe (dppe = 1,2-bis-(difenilfosfino)etano), conduce al clúster neutro $[Mo_3PtClS_4Cl_3(dppe)_3]$ con un rendimiento del 37%, mientras que si se añaden 4 equivalentes de la misma difosfina, se forma el complejo $[Mo_3Pt(dppe)S_4Cl_3(dppe)_3]^+$ con un 29% de rendimiento.[55] Un año más tarde, Sykes y colaboradores hacen

reaccionar el precursor acuo con una sal de platino (II), concretamente $K_2[PtCl_4]$, en presencia de H_3PO_2, un agente reductor fuerte, y obtienen el clúster neutro $[Mo_3PtClS_4Cl_3(dppe)_3]$ en redimientos cercanos al 100%.[56] Ese mismo año Brorson y colaboradores preparan un clúster heterobimetálico de platino a partir del complejo $[Mo_3S_4(\eta_5\text{-}Cp')_3]^+$ mediante la estrategia [3+1]. La reacción del precursor trinuclear con el complejo $[Pt(nor)_3]$ (nor = 2-norborneno) resulta en el clúster $[Mo_3S_4Pt(nor)(\eta_5\text{-}Cp')_3]^+$ que, tratado posteriormente con trifenilfosfina, conduce al compuesto heterobimetálico de fórmula $[Mo_3Pt(PPh_3)S_4(\eta_5\text{-}Cp')_3]^+$ con un 92 % de rendimiento.[57]

En el presente trabajo de investigación, se ha desarrollado una estrategia de síntesis similar para incorporar platino a la unidad Mo_3S_4 funcionalizada con diaminas. Tal como se representa en el esquema 3, el clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ se hace reaccionar con el complejo $Pt(PPh_3)_4$ en THF para dar lugar al clúster heterobimetálico $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ con un rendimiento del 52%.



Esquema 3. Síntesis del clúster $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ mediante la metodología de construcción por bloques [3+1].

La reacción transcurre a temperatura ambiente con un cambio de color inmediato de verde a marrón tras la adición de $Pt(PPh_3)_4$. El producto precipita en el seno de la reacción y, tras filtrar y lavar con THF frío, el sólido marrón obtenido se caracteriza por las técnicas espectroscópicas y espectrométricas habituales como $[Mo_3Pt(PPh_3)S_4(dmen)_3](BF_4)$, cuya estructura se determina por difracción de rayos

X en monocristal. La Figura 5 muestra una representación ORTEP de la estructura del catión $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$.

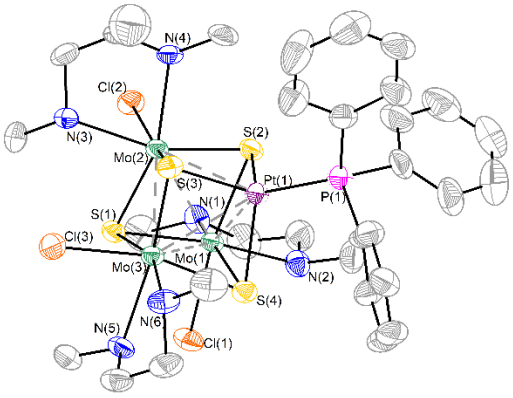


Figura 5. Representación ORTEP del clúster $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ (elipsoides al 50% de probabilidad).

El clúster $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ cristaliza en el grupo espacial $P2_1/c$, donde los átomos metálicos de la unidad Mo_3PtS_4 ocupan los vértices de un tetraedro ligeramente distorsionado con cada una de sus caras apuntadas por átomos de azufre. En la Tabla 2 se muestran las distancias más representativas del catión $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ junto a las de los dos únicos complejos Mo_3PtS_4 caracterizados estructuralmente hasta la fecha.

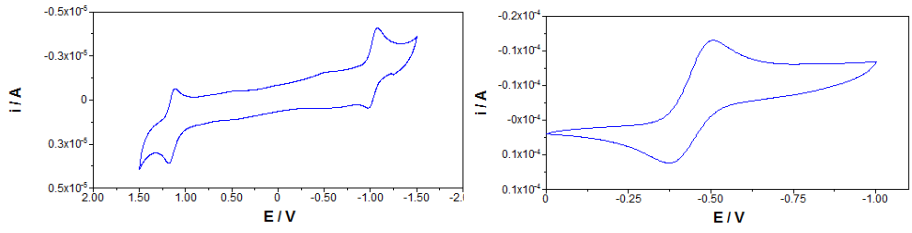
La inserción de platino no produce cambios estadísticamente significativos en las distancias Mo-Mo y Mo-Cl respecto a las del clúster trinuclear de partida. Dicha incorporación produce una elongación de las distancias Mo-(μ-S) del clúster trinuclear de 2.29 Å a 2.352 Å, ahora representadas como Mo-($\mu_{3(2Mo\text{-}Pt)}$-S) debido a que los azufres puente pasan a ser tridentados y apuntan a dos átomos de molibdeno y a uno de platino.

Tabla 2. Selección de distancias de enlace promedio para los compuestos $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$, $[Mo_3Pt(PPh_3)S_4(\eta_5\text{-}Cp')_3]^+$ y $[Mo_3PtClS_4Cl_3(dppe)_3]$.

Distancia (Å)	**$[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$**	**$[Mo_3Pt(PPh_3)S_4(\eta_5\text{-}Cp')_3]^+$[a]**	**$[Mo_3PtClS_4Cl_3(dppe)_3]$[b]**
Mo-Mo	2.775[6]	2.837[2]	2.817[3]
Mo-Pt	2.836[4]	2.861[2]	2.755[2]
Mo-($\mu_{3(3Mo)}$-S)	2.333[1]	2.315[5]	2.347[4]
Mo-($\mu_{3(2Mo\text{-}Pt)}$-S)[c]	2.352[2]	2.338[5]	2.353[2]
Mo-($\mu_{3(2Mo\text{-}Pt)}$-S)[d]	2.352[7]		2.376[8]
Pt-($\mu_{3(2Mo\text{-}Pt)}$-S)	2.354[4]	2.371[5]	2.331[7]
Mo-Cl	2.517[10]	----------	2.484[7]
Pt-P	2.262(2)	2.232(4)	----------

[a]Datos extraídos de la referencia [57]. [b]Datos extraídos de la referencia [55]. [c]Distancia *trans* al enlace Mo-Cl. [d]Distancia *trans* al enlace Mo-N/P. ( ) Desviación estándar de la medida. [ ] Desviación estándar del promedio.

Desde el punto de vista electrónico, la incorporación de platino en la unidad trinuclear produce un cambio en las poblaciones electrónicas del clúster. Así, la unidad Mo_3^{12+} con sus seis electrones metálicos para formar tres enlaces sencillos metal-metal, pasa a ser una unidad Mo_3Pt^{12+} con 16 electrones metálicos. Por lo tanto, cabe esperar cambios en las propiedades redox, las cuales se han investigado mediante voltametría cíclica. La Figura 5 muestra los voltagramas cíclicos de los clústeres $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ y $[Mo_3S_4Cl_3(dmen)_3]^+$. En el primero de ellos, se observa una onda de reducción y otra de oxidación de intensidades similares, mientras que el clúster trinuclear presenta una única onda de reducción. El comportamiento del complejo tetranuclear es análogo al del clúster Mo_3PtS_4 con ligandos Cp', en el que también se producen procesos redox atribuidos a la oxidación bielectrónica y reducción monoelectrónica del clúster. En nuestro caso, en ausencia de experimentos adicionales, no es posible asignar el número de electrones involucrados en cada proceso, aunque a la vista de las intensidades, cabe esperar que la reducción y la oxidación del clúster involucren el mismo número de electrones.



(a) (b)

Figura 5. Voltagramas cíclicos de los clústeres $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ (a) y $[Mo_3S_4Cl_3(dmen)_3]^+$ (b) en diclorometano a 100 mV/s (*vs* Ag/AgCl).

La Tabla 3 lista los potenciales rédox de los clústeres diamino Mo_3S_4 y Mo_3PtS_4 junto a los publicados para clústeres análogos derivados con Cp'. El complejo trinuclear amino muestra una onda de reducción a -0.45 V sin que se aprecie ningún proceso de oxidación dentro del rango que limita el disolvente. La inserción de platino en el clúster diamino produce un desplazamiento catódico de la onda de reducción de 0.57 V, tendencia similar a la observada al incorporar platino en el clúster $[Mo_3S_4(\eta_5\text{-}Cp')_3]^+$, aunque en este último caso el desplazamiento es menos acusado (0.26 V). Además, también se produce la aparición de un proceso de oxidación que no se observa en el complejo trinuclear. Es decir, la inserción de platino en la unidad Mo_3S_4 resulta en compuestos más fáciles de oxidar y más difíciles de reducir.

Tabla 3. Potenciales electroquímicos de los clústeres $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$, $[Mo_3Pt(PPh_3)S_4(\eta_5\text{-}Cp')_3]^+$ y sus precursores en diclorometano.

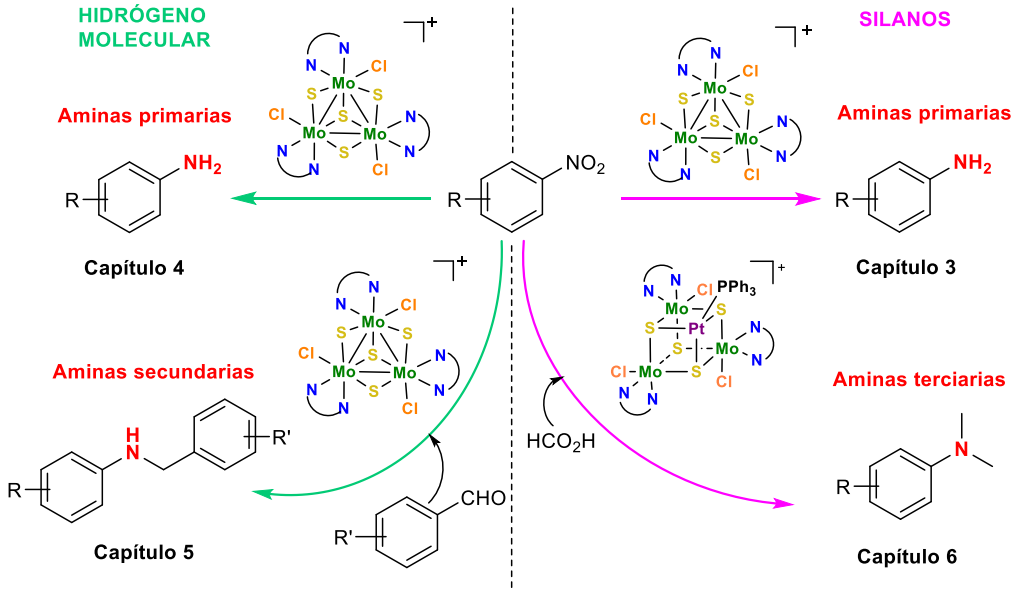
Compuesto	Oxidación	Reducción
	$E_{1/2}(\Delta E^*)$ (V)	$E_{1/2}(\Delta E^*)$ (V)
$[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ [a]	1.15(0.06)	-1.02(0.08)
$[Mo_3S_4Cl_3(dmen)_3]^+$ [a]	-	-0.45(0.13)
$[Mo_3Pt(PPh_3)S_4(\eta_5\text{-}Cp')_3]^+$ [b]	0.79(0.09)	-1.07(0.06)
$[Mo_3S_4(\eta_5\text{-}Cp')_3]^+$ [b]	1.19(0.09)	-0.81(0.09)

[a] $E_{1/2}$ (Fc/Fc^+) = 0.44 V *vs* Ag/AgCl. [b] $E_{1/2}$ (Fc/Fc^+) = 0.40 V *vs* SCE. * $\Delta E = |E_c - E_a|$

7.3. Aplicaciones catalíticas de los clústeres Mo_3S_4 y Mo_3PtS_4

La investigación de esta tesis doctoral se ha dirigido hacia la obtención de aminas primarias, secundarias y terciarias mediante reducción catalítica de nitroarenos. Como catalizadores hemos utilizado compuestos trinucleares Mo_3S_4 y heterobimetálicos Mo_3PtS_4 funcionalizados con ligandos diamina y diimina. La metodología de trabajo ha sido análoga en todos los sistemas catalíticos estudiados a lo largo de esta tesis. En primer lugar, se han optimizado las condiciones de reacción para conseguir conversiones completas y rendimientos cuantitativos mediante condiciones suaves y/o sostenibles. A continuación, se ha evaluado la selectividad del proceso, característica muy importante en el desarrollo de nuevos catalizadores y que hoy en día supone un reto a nivel industrial. Además, se ha llevado a cabo, en la medida de lo posible, un seguimiento de las reacciones dirigido a explorar sus mecanismos y demostrar la integridad de la unidad clúster durante el proceso. Las técnicas experimentales utilizadas con este fin han sido la espectroscopía de RMN y/o la espectrometría de masas (ESI-MS), en ocasiones realizada mediante la técnica de infusión de muestra presurizada (*PSI*), que ha permitido la monitorización del proceso. Finalmente, se han realizado experimentos a partir de distintos intermedios orgánicos con el fin de discernir entre las posibles rutas de reacción.

Los cuatro procesos catalíticos estudiados durante la realización de este trabajo de investigación para la síntesis de aminas primarias, secundarias y terciarias, se resumen en el Esquema 4. En dos de ellos, la reducción se ha llevado a cabo con hidrógeno molecular, el agente reductor más benévolo con el medioambiente. En los otros dos trabajos, el hidrógeno molecular se ha sustituido por silanos que, aunque presentan el inconveniente de generar bastantes residuos, permiten llevar a cabo la catálisis mediante condiciones más suaves y sin utilizar equipos a presión.

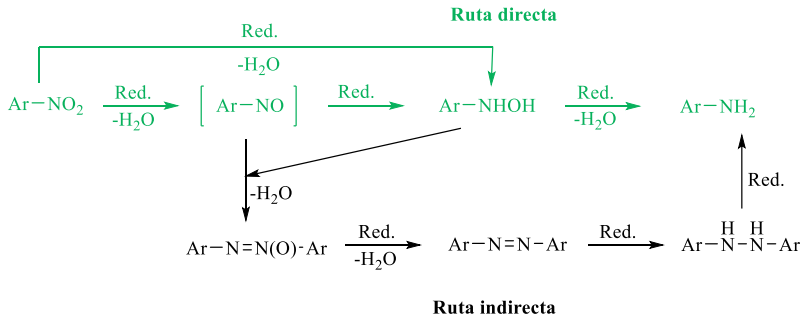


Esquema 4. Resumen de los procesos catalíticos estudiados en la presente tesis doctoral.

La reducción de nitroarenos catalizada por el clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ en presencia de silanos se describe en el Capítulo 3 de esta tesis doctoral. Los aspectos más destacados son las condiciones suaves a las que se trabaja (temperatura ambiente y presión atmosférica) y la elevada selectividad del catalizador. Además, se hace hincapié en demostrar la integridad de la unidad clúster durante el proceso catalítico. Para ello, se utiliza la técnica de infusión de muestra presurizada (*PSI*) en combinación con espectrometría de masas, que nos permite hacer un seguimiento de las especies clúster que aparecen durante la reacción. Cabe destacar que, durante todo el proceso, el pico molecular asociado al clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ se mantiene, y no existen evidencias experimentales de que el tratamiento con silanos genere especies hidruro por sustitución de los ligandos cloro terminales. La formación de estas especies es clave en la reducción de nitroarenos catalizada por el clúster $[Mo_3S_4Cl_3(dmpe)_3]^+$ (Figua 2).[28] Además, la posibilidad de generación de vacantes de coordinación

mediante descoordinación de un átomo de nitrógeno de la diamina, mecanismo propuesto para la hidrodefluoración catalizada por el clúster $[Mo_3S_4H_3(dmpe)_3]^+$, ha sido descartada.[58] Los cálculos teóricos realizados por el Profesor Vicent Sixte Safont de la Universitat Jaume I, determinan una barrera energética (ΔG) de 27 Kcal/mol, incompatible con un proceso catalítico que opere a temperatura ambiente. En la actualidad, se están realizando más estudios teóricos con el fin de determinar los posibles intermedios clúster que se generan durante este proceso catalítico.

Además de indagar en las especies clúster involucradas en el proceso catalítico, también se han investigado los diferentes caminos propuestos para la reducción de nitroarenos a anilinas. En la literatura se describen dos posibles rutas para este proceso: la ruta directa (color verde, Esquema 5) y la indirecta.[59,60] Además, existen dos variantes de la ruta directa, una que consiste en tres procesos de reducción a través de la formación consecutiva de nitrosoareno (Ar-NO) e hidroxilamina (Ar-NHOH) antes de generar la anilina, y otra variante en la que la reducción tiene lugar sin la formación previa de nitrosoareno. Por su parte, la ruta indirecta implica la condensación de nitrosoareno e hidroxilamina para dar lugar al derivado azoxiareno (Ar-N=N(O)-Ar), el cual se reduce vía la formación del azoareno (Ar-N=N-Ar) y de la 1,2-difenil-hidracina (Ar-NH-NH-Ar), obteniéndose finalmente la anilina ($Ar-NH_2$).



Esquema 5. Posibles rutas de reacción para la reducción de nitrobenceno a anilina. Ruta directa marcada en verde.

Con el fin de investigar la ruta a través de la cual tiene lugar la reducción de nitroarenos catalizada por el clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ en presencia de silanos, la reacción se lleva a cabo a partir de algunos de los intermedios propuestos en ambas rutas. Los resultados concluyen que el proceso transcurre por la ruta directa, ya que la reacción catalítica no funciona cuando el sustrato de partida es el azoxibenceno. Este estudio, además de aportar pistas sobre el camino de reacción, nos ha permitido descubrir que el clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ cataliza también la reducción de azoarenos con altas conversiones y rendimientos.

Para evaluar la selectividad del catalizador, hemos partido de nitroarenos y azoarenos que contienen otros grupos funcionales. Cabe destacar que, el sistema catalítico desarrollado, es capaz de reducir selectivamente el grupo nitro o azo en presencia incluso de grupos fácilmente reducibles tales como dobles enlaces, cetonas o grupos derivados de los ácidos carboxílicos.

La obtención de aminas primarias mediante la reducción de nitroarenos con hidrógeno molecular se describe en el Capítulo 4 de esta tesis. En este caso, tanto el clúster diamino $[Mo_3S_4Cl_3(dmen)_3]^+$ como el derivado diimino $[Mo_3S_4Cl_3(dnbpy)_3]^+$, son catalizadores o precatalizadores eficientes en la reducción de nitroarenos a 20 bar de presión de hidrógeno y 70 ºC. La quimioselectividad se ha estudiado más extensamente que en el caso de la reducción con silanos y hemos demostrado que el sistema catalítico permite obtener más de 30 anilinas funcionalizadas de gran interés en la industria química y en medicina. Cabe destacar que, el clúster funcionalizado con diiminas, precisa de un disolvente prótico para catalizar este proceso, concretamente metanol. En los intentos llevados a cabo para demostrar la integridad de este clúster mediante espectrometría de masas, se observan picos correspondientes a las especies $[Mo_3S_4Cl_3(dnbpy)_3]^+$ y $[Mo_3S_4Cl_{3-x}(OMe)_x(dnbpy)_3]^+$, manteniéndose la unidad trinuclear Mo_3S_4. Por otro lado, el clúster diamino es activo en un amplio rango de disolventes, como tetrahidrofurano y acetonitrilo. En este caso, la

monitorización de la reacción por espectrometría de masas demuestra la integridad del complejo $[Mo_3S_4Cl_3(dmen)_3]^+$, tal y como ocurría en la reducción con silanos. Ante la dificultad de identificar las especies catalíticamente activas, actualmente se están realizando cálculos computacionales que sugieren que los azufres puente del clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ juegan un papel clave en el proceso catalítico. Estudios teóricos recientes sobre la evolución de hidrógeno a partir de agua catalizada por clústeres aniónicos Mo_3S_4 avalan esta hipótesis.[61]

Por otro lado, en este trabajo de hidrogenación catalítica también se han realizado una serie de experimentos para discernir entre las dos posibles rutas de reacción que se representan en el Esquema 5. En este caso, ambos caminos son posibles, pero un análisis cinético de la evolución de los intermedios orgánicos con el tiempo ha confirmado que la ruta directa es la más rápida y, por tanto, la que tendrá lugar de manera mayoritaria.

Tras el éxito obtenido en la síntesis catalítica de aminas primarias mediante hidrogenación directa o hidrosililación bajo condiciones suaves, se decidió abordar la síntesis de aminas secundarias y terciarias. Generalmente, su preparación requiere la síntesis y purificación de las aminas primarias y su posterior funcionalización para generar las aminas secundarias y terciarias deseadas. En este contexto, el diseño de metodologías en tándem que permitan la utilización de compuestos nitro como sustratos de partida, abordado en los Capítulos 5 y 6 de esta tesis, es indudablemente más ventajoso.

Los procesos en cascada o tándem, en los que se combinan distintas reacciones en una única operación sintética, evitan la separación y purificación de intermedios, de manera que los residuos generados son escasos. Por este motivo, la catálisis en tándem es hoy en día una alternativa excelente en la búsqueda de reacciones más económicas y sostenibles que permitan la obtención de productos valiosos a partir de otros más abundantes y baratos. Existen multitud de clases de

procesos tándem en función del número de ciclos implicados, el número de especies catalíticas o la distribución de los reactivos y los productos en los ciclos, dos ejemplos de los cuales se representan en la Figura 6. En el primero, es la misma especie la que cataliza los dos procesos implicados, mientras que en el segundo intervienen dos catalizadores o fragmentos metálicos distintos.[62]

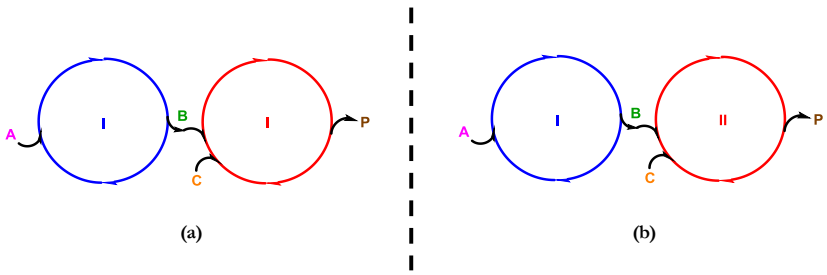
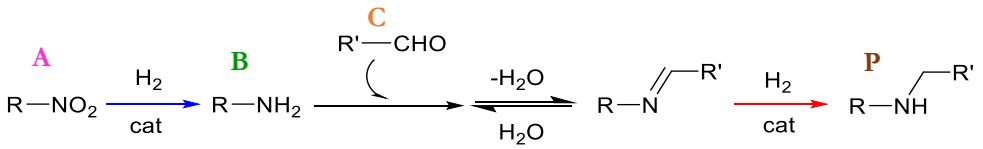


Figura 6. Representación esquemática de dos clases de procesos catalíticos tándem utilizando una (a) o dos (b) especies catalíticas.

El proceso de aminación reductiva en tándem catalizado por el clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ se describe en el Capítulo 5 de esta tesis. En este proceso, es el mismo complejo el que cataliza, en primer lugar, la reducción del compuesto nitro (A) y, en segundo lugar, la reducción del intermedio imino procedente de la condensación entre la amina primaria (B) y el aldehído (C), tal como se ilustra en el Esquema 7.



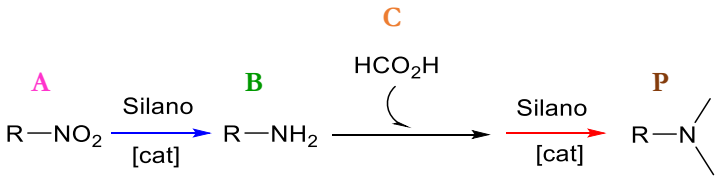
Esquema 7. Representación esquemática de la aminación reductiva a partir de compuestos nitro mediante un proceso de catálisis tándem.

Los sustratos de partida utilizados en este protocolo son económicos y la reducción se produce con hidrógeno molecular, por lo que se trata de un proceso eficiente y respetuoso con el medioambiente para la obtención de aminas secundarias.

Cabe destacar que, a pesar de que el agua es un producto de la reacción orgánica y sería esperable que su eliminación desplazara el equilibrio hacia la derecha aumentando la velocidad de la reacción, el uso de tamices moleculares que atrapen el agua disminuye la conversión a la mitad, sin observarse formación del producto deseado. Un estudio minucioso en el que se añaden cantidades conocidas de agua en el disolvente de la reacción pone de manifiesto que son necesarias trazas de ésta (150 – 1500 ppm) para que los resultados sean óptimos, ya que la ausencia o un exceso de la misma lleva a conversiones bajas o nulas. Estos resultados sugieren una implicación directa de las moléculas de agua en el mecanismo de la reacción, hecho que ya se ha descrito en la literatura para la aminación reductiva a partir de nitroarenos catalizada por nanopartículas de hierro o cobalto.[63-65]

Además, la selectividad del catalizador frente a otros grupos funcionales fácilmente reducibles es elevada, a pesar de que en algunos casos sea necesario utilizar condiciones de reacción un poco más drásticas (hasta 50 bar y 150 ºC). Tal y como ocurría tras la reacción de síntesis de aminas primarias con silanos o hidrógeno como agentes reductores, en este capítulo se ha demostrado mediante espectrometría de masas y RMN de protón que el clúster $[Mo_3S_4Cl_3(dmen)_3]^+$ se mantiene tras el proceso de aminación reductiva, por lo que nos encontramos ante otro ejemplo de catálisis mediada por clústeres.

La obtención de aminas terciarias, más específicamente de anilinas dimetiladas, se describe en el Capítulo 6 de esta tesis. En este caso, su preparación se lleva a cabo por metilación directa del correspondiente nitroareno utilizando ácido fórmico y fenilsilano como agentes metilante y reductor, respectivamente (Esquema 8). Cabe destacar que los ejemplos en los que se lleva a cabo la preparación de anilinas dimetiladas mediante reacciones en tándem a partir de nitroarenos son muy escasos, y en general utilizan condiciones de reacción bastante severas sin que haya quedado demostrada su selectividad.



Esquema 8. Representación esquemática de la metilación directa de nitrocompuestos mediante un proceso de catálisis tándem.

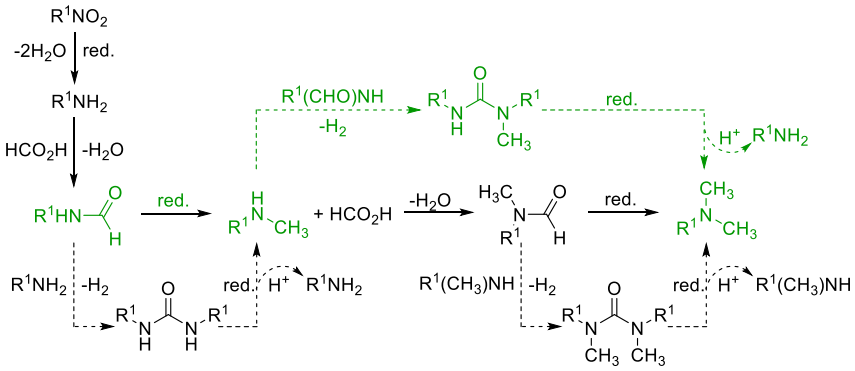
Para abordar con éxito este proceso catalítico en tándem, se diseñó un clúster heterobimetálico Mo_3PtS_4 que combinase la actividad catalítica de la unidad Mo_3S_4 en la reducción de nitroarenos con la del platino en las reacciones de metilación de aminas.[66–68] Aunque en un principio se postuló que el fragmento Mo_3S_4 catalizaría la primera etapa de la reacción y el platino la segunda, un estudio exhaustivo demostró que ambos metales participan en los dos procesos, siendo más activo el fragmento trinuclear de molibdeno en la primera etapa y el platino en la segunda.

El clúster $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ cataliza la metilación directa de nitroarenos de un modo muy eficaz y bajo condiciones de reacción suaves (70 ºC, presión atmosférica). Este clúster heterobimetálico puede prepararse *in situ* por reacción del clúster trinuclear $[Mo_3S_4Cl_3(dmen)_3]^+$ (3 mol%) y el complejo $Pt(PPh_3)_4$ (1 mol%), dando lugar de forma inmediata a una mezcla de los complejos clúster $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ y $[Mo_3S_4Cl_3(dmen)_3]^+$ en el medio de reacción. Bajo estas condiciones de exceso de clúster trinuclear se favorece la consecución de la primera etapa, es decir, la reducción del nitroareno a la anilina, permitiendo llevar a cabo la reacción global a temperatura ambiente o en tiempos de reacción menores.

La mezcla Mo_3S_4/Mo_3PtS_4 cataliza de manera selectiva la reducción del grupo nitro a anilina y la consiguiente metilación de la misma en presencia de grupos tanto dadores como aceptores de electrones, de halógenos y de grupos fácilmente reducibles. Además, este nuevo sistema catalítico también permite la metilación

directa de compuestos nitro bencílicos para dar lugar a las correspondientes aminas bencílicas dimetiladas.

El Esquema 9 resume las posibles rutas de reacción para la metilación directa de nitroarenos. La obtención de la amina dimetilada a partir de la especie formamida en ausencia de ácido fórmico confirma que la reacción puede transcurrir también a través de la formación de especies urea (ruta marcada en verde en el Esquema 9).



Esquema 9. Rutas de reacción propuestas para la metilación directa de nitroarenos con ácido fórmico y silanos.

En conclusión, los sulfuros clúster de molibdeno son catalizadores eficientes y selectivos en procesos dirigidos a la obtención de aminas. Concretamente, los clústeres Mo_3S_4 funcionalizados con ligandos diamina y diimina catalizan bajo condiciones suaves la reducción de nitroarenos, tanto en presencia de silanos como de hidrógeno molecular, para formar anilinas en altos rendimientos. Estos clústeres son también excelentes catalizadores en la reacción de aminación reductiva de aldehídos con nitro compuestos, dando lugar a las correspondientes aminas secundarias de un modo muy eficiente. Por último, la incorporación de un átomo de platino a la unidad Mo_3S_4 ha permitido ampliar su aplicación hacia la preparación de aminas terciarias mediante la metilación directa de nitroarenos con ácido fórmico en un proceso tándem.

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8

Concluding remarks

8. Concluding remarks

"La ciencia no es sólo una disciplina de razón, sino también de romance y pasión."

Stephen Hawking

The following conclusions can be drawn from the results presented in this PhD Thesis:

(i) Coordination of diamine ligands to the Mo_3S_4 cluster core is carried out in a one-pot two-step procedure starting from the $[Mo_3S_7Cl_6]^{2-}$ ion to obtain the novel complex $[Mo_3S_4Cl_3(dmen)_3]^+$ (dmen = *N,N'*-dimethilethylenediamine).

(ii) The substitution of labile thiourea (tu) molecules in the $[Mo_3S_4(tu)_8(H_2O)^{4+}$ complex affords the new diimino $[Mo_3S_4Cl_3(dnbpy)_3]^+$ (dnbpy = 4,4'-dinonyl-2,2'-dipyridyl) cluster. This procedure is also extended to the synthesis of the diamino $[Mo_3S_4Cl_3(dmen)_3]^+$ complex.

(iii) The new diamino and diimino Mo_3S_4 clusters present a C_3 symmetry and both are obtained as single chiral isomers with one of the nitrogen atoms *trans* to the capping sulphur and the other one *trans* to the bridging sulphur. Both clusters are characterized by elemental analyses, mass spectrometry and nuclear magnetic resonance spectroscopy.

(iv) The structure of the diamino complex is determined by X-ray diffraction and the metal-metal and metal-sulfphur distances in the Mo_3S_4 core follow the same tendencies observed for analogous diphosphino and aminophosphino complexes.

(v) The $[Mo_3S_4Cl_3(dmen)_3]^+$ cluster is an excellent catalyst for the reduction of diverse nitro and azoarenes under mild conditions using silanes as reducing agents.

(vi) This new catalyst is highly chemoselective and twenty-five structurally diverse anilines are obtained in good to excellent yields from nitro- and azocompounds bearing other easily reducible functional groups.

(vii) Reaction monitoring using a pressurized sample infusion (PSI) ESI mass spectrometric technique demonstrates that the integrity of the cluster

core remains during the catalytic reaction. Moreover, reduction of different potential intermediates suggests that formation of aniline proceeds preferentially through the direct reduction route via the nitrosoarene and the hydroxylamine derivatives formation.

(viii) Unlike diphosphino or aminophosphino Mo_3S_4 complexes, their diamino or diimino analogous are active reduction catalysts under hydrogen pressure. The $[Mo_3S_4Cl_3(dnbpy)_3]^+$ complex catalyzes the reduction of nitroarenes under 20 bar of hydrogen pressure and 70 ºC to selectively afford more than 30 primary amines of interest in medicine and industry.

(ix) Reaction monitoring by electrospray ionization mass spectrometric measurements shows the integrity of the cluster unit during the catalytic hydrogenation. The analysis of the evolution of different key intermediates with reaction time gives support to the direct route sequence.

(x) The diamino $[Mo_3S_4Cl_3(dmen)_3]^+$ cluster is highly selective for the catalytic one-pot reductive amination of aldehydes starting from nitroarenes to afford a wide range of secondary amines using hydrogen as reductant. This "green" process applies for aromatic as well as for aliphatic nitro compounds and aldehydes. Spectrometric and spectroscopic techniques show no fragmentation of the cluster during the catalytic reaction.

(xi) The [3+1] building-block strategy allows to incorporate platinum into the trinuclear $[Mo_3S_4Cl_3(dmen)_3]^+$ complex to yield the heterobimetallic $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3](BF_4)$ cluster salt. The new complex is characterized by elemental analyses, mass spectrometry, nuclear magnetic resonance spectroscopy and its structure is determined by X-ray diffraction techniques.

(xii) The electrochemical properties of the heterobimetallic complex and its

trinuclear precursor are investigated by cyclic voltammetry. The incorporation of the Pt-PPh_3 moiety exerts an important electronic influence so that the tetranuclear $[Mo_3Pt(PPh_3)S_4Cl_3(dmen)_3]^+$ complex is more difficult to reduce and easier to oxidize than its trimetallic precursor.

(xiii) In the presence of the heterobimetallic Mo_3PtS_4 cluster, the direct methylation of nitroarenes has been successfully accomplished at 70 ºC using formic acid as a renewable C_1 source and silanes as reducing agents. An excess of the trinuclear $[Mo_3S_4Cl_3(dmen)_3]^+$ complex favors the first step of the tandem reaction, that is, the reduction of the nitro compound to aniline, thus permitting to perform the full catalytic process at room temperature and/or lower reaction times.

(xiv) A large variety of aromatic tertiary amines, some of them containing easily reducible moieties, have been obtained in good to quantitative yields (66-99 %). In addition, a benzylic-type nitro compound is also effectively reduced to the corresponding amine.